CAREPATHrx™
Specialty Pharmacy & Infusion Solutions

CLINICAL GUIDELINES FOR INTRAVENOUS INFLIXIMAB AND BIOSIMILARS

Section: Nursing
Compliance: ACHC Infusion Pharmacy
ACHC Standards:
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I. SUMMARY/REVIEW

Infliximab (Remicade) is a chimeric monoclonal antibody that binds to human tumor necrosis factor alpha (TNFα), thereby interfering with endogenous TNFα activity. Infliximab is indicated for several disease states such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease and ulcerative colitis, which is characterized by increased TNFα in involved tissues or fluids. TNFα is known to induce pro-inflammatory cytokines (interleukins), enhance leukocyte migration, activate neutrophils and eosinophils, and induce acute phase reactants and tissue degrading enzymes.

Biosimilars: A biosimilar product is highly similar and has no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from an existing FDA-approved reference product. The manufacturer of a proposed biosimilar product generates data comparing the proposed product to the FDA-approved reference product to demonstrate biosimilarity. A manufacturer that shows its proposed biosimilar product is highly similar may rely in part on FDA's previous determination of safety and effectiveness for the reference product for approval. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients. Biosimilar products may have different inactive or excipient ingredients than the reference product.

Multiple biosimilars for Infliximab (Remicade®) are available in the United States (i.e Inflectra® (infliximab-dyyb), Renflexis® (infliximab-adba), Avsola® (infliximab- axxq). When dispensing biosimilar products, the four-letter suffix (ex: infliximab- **dyyb**) must be present after the generic drug name to distinguish which biosimilar product is dispensed.

II. PHARMACOLOGY OVERVIEW

A. Indications

1. Treatment of adults with active ankylosing spondylitis;
2. Treatment of adults and children ≥ 6 years with moderately- to severely active Crohn's disease with inadequate response to conventional therapy;

3. Treatment of adults with chronic severe plaque psoriasis as an alternative to other systemic therapy;
4. Treatment of adults with psoriatic arthritis;
5. Treatment of adults with moderately- to severely- active rheumatoid arthritis;
6. Treatment of adults and children ≥ 6 years with moderately- to severely active ulcerative colitis with inadequate response to conventional therapy.

B. Contraindications - Hypersensitivity to infliximab, murine proteins, or any component of the formulation; doses>5 mg/kg in patients with moderate or severe heart failure (NYHA Class III/IV)

C. Patient Acceptance/Exclusion Criteria

1. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon Chartwell Pennsylvania's admission criteria.
2. The decision to administer a first dose in the home by a Chartwell field nurse will be determined on a case-by-case basis and reviewed by nursing and pharmacy management. The following criteria will be evaluated:
    a. Prescriber preference
    b. Allergy profile
    c. Age ≥18 years
    d. Ability to secure contracted nursing for subsequent infusions
    e. Other relevant social and/or medical history
3. Chartwell treatment protocol for anaphylaxis will be instituted unless more comprehensive patient-specific orders are provided by physician. See policy NUR012.

D. Precautions

1. Autoimmune Disorder
    a. Positive antinuclear antibody titers have been detected in patients, with negative baseline; rare cases of autoimmune disorder, including lupus-like syndrome, have been reported. Monitor and discontinue if symptoms develop

2. Cardiovascular and Cerebrovascular Reactions
    a. Transient visual loss has been reported during or within two hours of infusion. Myocardial ischemia/infarction, hypotension, hypertension, and arrythmias may occur within 24 hours of infusion. Review medical history prior to initiation and monitor before and immediately after infusion.

3. Hematologic disorders
    a. Hematologic toxicities have been reported. Use in caution with patients with history of hematologic abnormalities

4. Hepatic Reactions
    a. Severe hepatic reactions have been reported during treatment, occurred between 2 weeks to > 1 year after initiation of therapy and some cases were fatal or necessitated

liver transplantation. Discontinue with jaundice and/or increased liver enzymes (> 5 times ULN)

5. Hepatitis B Virus
    a. Reactivation of hepatitis B virus has occurred in chronic carriers of the virus.

6. Hypersensitivity
    a. Serious infusion reactions including anaphylaxis or serum sickness like reactions may occur.

7. Infusion Reactions
    a. Acute infusion reactions may occur. Hypersensitivity reaction may occur within 2 hours of infusion. Medication and equipment for management of hypersensitivity reaction should be available for immediate use. Consider pretreatment, may be warranted in all patients with prior infusion reactions.

8. Infection
    a. Patients receiving infliximab are at increased risk for serious infection which may result in hospitalization and/or fatality. Active tuberculosis, invasive fungal and bacterial, viral or other opportunistic infections have been reported. Monitor closely for signs/symptoms of infection. Discontinue for serious infection or sepsis. Consider risks versus benefits prior to use in patients with a history of chronic or recurrent infection. Consider empiric antifungal therapy in patients who are at risk for invasive fungal infection and develop severe systemic illness.

9. Malignancy
    a. [US Boxed Warning]: Lymphoma and other malignancies (may be fatal) have been reported in children and adolescent patients receiving TNF-blocking agents including infliximab.
    b. [US Boxed Warning]: Post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with infliximab. Almost all patients had received concurrent or prior treatment with azathioprine or mercaptopurine at or prior to diagnosis and the majority of reported cases occurred in adolescent and young adult males with Crohn disease or ulcerative colitis.

10. Tuberculosis
    a. [US Boxed Warning]: Infliximab treatment has been associated with active tuberculosis (may be disseminated or extra pulmonary) or reactivation of latent infections. Evaluate patients for tuberculosis risk factors and latent tuberculosis infection (with a tuberculin skin test) prior to and during therapy. Treatment of latent tuberculosis should be initiated before use. Patients with initial negative tuberculin skin tests should receive continued monitoring for tuberculosis throughout treatment.

11. Lactation - excreted in breast milk. Not recommended
    a. Infliximab was detected within 12 hours and the highest milk concentrations were seen 2-3 days after the dose. Due to the potential for serious adverse reactions in the nursing infant,

the manufacturer recommends a decision be made whether to discontinue nursing or to discontinue the drug, considering the importance of treatment to the mother.

E. Pharmacokinetics
1. Onset of action: ~ 2 weeks
2. Volume of distribution is 3-6 L, at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment.
3. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of infliximab, median serum concentrations ranged from approximately 0.5 to 6 mcg/mL; Development of antibodies to infliximab increased clearance, resulting in undetectable serum concentration.
4. Half-life elimination: 7- 12 days

F. Adverse Reactions
1. Rheumatoid Arthritis
   a. Headache 18%
   b. GI: Nausea 21%; Diarrhea 12%; Abdominal pain 12%
   c. Increased serum ALT - risk increased with concomitant use of methotrexate
   d. Increased ANA titer ~50%
   e. Infection 36%
   f. Respiratory: Upper respiratory tract infection 32%; Sinusitis 14%; Cough 12%; Pharyngitis 12%
   g. Infusion related reaction 20%; (1) Severe < 1%

2. Crohn's Disease
   a. Hepatic: Increased liver enzymes 18%; (1) ≥5 times ULN 1%
   b. Anemia 11%
   c. Infection 56% (more common with every 8-week vs every 12-week infusions)

G. Drug Interactions
1. Bacillus Calmette–Guérin, vaccine and intravesical - Risk X: Avoid Combination
   a. Immunosuppressants may diminish the therapeutic effect of BCG.

2. Calcineurin Inhibitor - Risk X: Avoid combination
   a. Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants.
   b. Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants.

3. Janus Associated Kinase Inhibitor - Risk X: Avoid Combination
   a. Tofacitinib: Anti-TNF Agents may enhance the adverse/toxic effect of Tofacitinib.
   b. Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib.
   c. Management: Concurrent use with ant rheumatic doses of methotrexate or nonbiologic disease modifying ant rheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants.

4. Interleukin 1 Receptor antagonist - Risk X: Avoid Combination
    a. Anakinra: Anti-TNF Agents may enhance the adverse/toxic effect of Anakinra. An increased risk of serious infection during concomitant use has been reported.
    b. Canakinumab: Anti-TNF Agents may enhance the adverse/toxic effect of Canakinumab. Specifically, the risk for serious infections and/or neutropenia may be increased.
    c. Rilonacept: Anti-TNF Agents may enhance the adverse/toxic effect of Rilonacept.
    d. Tocilizumab: May enhance the immunosuppressive effect of Anti-TNF Agents.
    e. Ustekinumab: May enhance the immunosuppressive effect of InFLIXimab.

5. Monoclonal Antibody - Risk X: Avoid combination
    a. Belimumab: Monoclonal Antibodies may enhance the adverse/toxic effect of Belimumab.

6. Selective Adhesion-Molecule Inhibitor
    a. Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. Risk X: Avoid combination
    b. Vedolizumab: Anti-TNF Agents may enhance the adverse/toxic effect of Vedolizumab.

7. Selective T Cell Costimulation Modulator - Risk X: Avoid Combination
    a. Abatacept: Anti-TNF Agents may enhance the adverse/toxic effect of Abatacept. An increased risk of serious infection during concomitant use has been reported.

8. TNF Blocking Agent - Risk X: Avoid Combination
    a. Adalimumab: May enhance the immunosuppressive effect of InFLIXimab.
    b. Certolizumab Pegol: Anti-TNF Agents may enhance the immunosuppressive effect of Certolizumab Pegol.
    c. Etanercept: May enhance the immunosuppressive effect of InFLIXimab.
    d. Golimumab: May enhance the immunosuppressive effect of InFLIXimab.

9. Vaccines
    a. Live - Risk X: Avoid Use
    b. Immunosuppressants may enhance the adverse/toxic effect of Vaccines. Immunosuppressants may diminish the therapeutic effect of Vaccines. Live attenuated vaccines should not be given for at least 3 months after immunosuppressants.

III. ADMINISTRATIVE GUIDELINES

A. Administration Guidelines
    1. Site: Intravenous infusion should begin within 3 hours of reconstitution and dilution. Do not infuse with other agents. Use in-line 0.2-micron low protein binding filter
    2. Rate: Given as IV infusion over at least 2 hours.

B. Dosage
    1. Adult Dosing

a. Ankylosing spondylitis: 5 mg/kg at 0, 2, and 6 weeks followed by 5 mg/kg every 6 weeks thereafter
b. Crohn's disease: 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter; dose may be increased to 10 mg/kg in patients who respond but then lose their response. If no response by week 14, consider discontinuing therapy.
c. Plaque psoriasis: 5 mg/kg at 0, 2, and 6 weeks followed by 5 mg/kg every 8 weeks thereafter
d. Rheumatoid arthritis (in combination with methotrexate therapy): 3 mg/kg at 0, 2, and 6 weeks, followed by 3 mg/kg every 8 weeks thereafter; Doses have ranged from 3 - 10 mg/kg repeated at 4-to-8-week intervals
e. Ulcerative colitis: 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter

2. Pediatric Dosing
   a. Crohn's disease: 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter. If no response by week 14, consider discontinuing therapy
   b. Ulcerative colitis: 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter

C. Duration
1. Duration of therapy should be dependent on patient response and adverse reaction. If no response is found after Week 14, discontinue treatment.

D. Dose Adjustment
1. Weigh risk vs. benefits for individual patient
2. NYHA Class I/II Heart Failure
   a. No dosage adjustment necessary; use in caution and monitor closely for worsening of HF
3. NYHA Class III or IV Heart Failure a) $\leq$ 5 mg/kg
4. Renal Impairment
   a. No dosage adjustment necessary
5. Hepatic Impairment
   a. No dosage adjustment necessary

IV. GUIDELINES FOR USE

A. Patient Monitoring
1. Monitor improvement of symptoms and physical function assessments.
2. Latent TB screening prior to initiating and during therapy;
3. Signs/symptoms of infection (prior to, during, and following therapy) ;
4. CBC with differential; Signs/symptoms/worsening of heart failure;
5. HBV screening prior to initiating (all patients), HBV carriers (during and for several months following therapy) ;
6. Symptoms of lupus like syndrome;
7. LFTs (discontinue if >5 times ULN) ;

8. Signs and symptoms of malignancy (e.g., splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss).
9. Psoriasis patients with history of phototherapy should be monitored for nonmelanoma skin cancer.
10. Infusion-related reactions
    a. Reaction Classification
        1) Mild Symptoms: rash, flushing, itching, myalgia, fever< 38 C^{o}/100.4 F^{o}
        2) Moderate: difficulty breathing, chest pains, hypertension, fever > 38 C^{o}/100.4 F^{o}
        3) Severe: hypotension, bronchospasms, angioedema
    b. Treatment of infusion reactions
        1) Mild -- Decrease infusion rate to 10 ml/hour. Initiate normal saline infusion (500 - 1000 ml/hour) and appropriate symptomatic treatment (see APPENDIX 1). Monitor vital signs every 10 minutes until normal. After 20 minutes, infusion may be increased at 15-minute intervals, as tolerated, to completion (initial increase to 20 ml/hr, then 40 ml/hr., then 80 ml/hr., to a max of 125 ml/hr.)
        2) Moderate -- Infusion should be stopped. Initiate normal saline infusion and appropriate symptomatic treatment (see APPENDIX 1). Monitor vital signs every 5 minutes until normal. After 20 minutes, infusion may be increased at 15-minute intervals, as tolerated, to completion (initial increase to 20 ml/hr, then 40 ml/hr, then 80 ml/hr, to a max of 125 ml/hr)
        3) Severe -- Infusion should be stopped. Administer appropriate symptomatic treatment (see APPENDIX 1). Monitor vital signs frequently. Contact physician. Re-treatment after a severe reaction should only be done if the benefits outweigh the risks and with appropriate prophylaxis in a controlled setting. These patients may no longer be a candidate for home infusion of future doses. Patients may be considered for home administration after a significant trial in a controlled environment with 3 successful infusions.
    c. Prophylaxis of infusion reactions:
        1) Premedication with acetaminophen and diphenhydramine 90 minutes prior to infusion may be considered in patients with prior infusion reactions. For patients with history of severe reactions, corticosteroid administration is recommended. In patients with cutaneous flushing, aspirin may be considered (Becker, 2004).
        2) Steroid dosing may be oral (prednisone 50 mg orally every 12 hours for 3 doses prior to infusion) or intravenous (a single dose of hydrocortisone 100 mg or methylprednisolone 20 to 40 mg administered 20 minutes prior to the infusion).
        3) Patients requiring a modified titration may benefit from a test dose at 10 mL/hour for 15 minutes. Thereafter, the infusion may be increased at 15-minute intervals, as tolerated, with a minimum administration time of two hours
    d. Delayed Infusion Reactions: Typically occur 1 to 7 days after an infusion.
        1) Treatment should consist of appropriate symptomatic treatment
        2) For delayed infusion reactions, pre-medicate with acetaminophen and diphenhydramine (dosing per physician order) 90 minutes prior to infusion. On initiation of the infusion, begin with a test dose at 10 mL/hour for 15 minutes. Thereafter, the infusion may be increased to infuse over 3 hours. Post infusion

therapy with acetaminophen for 3 days and an antihistamine for 7 days is recommended.

B. Overdose/Anaphylactic Guidelines

1. Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of over dosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

V. PHARMACY

A. How Supplied

1. Infliximab and biosimilars are provided as lyophilized 100mg drug per 20 mL vial for reconstitution with 10 mL SWFI. Refer to specific product packing and prescribing information for NDC, storage, stability, and excursion information.

B. Dispensing

1. Send appropriate number of infliximab vials for dose.
   a. Each vial contains 100mg of infliximab.
2. Send appropriate amount of SWFI for reconstitution of the vials of infliximab.
   a. Each vial of infliximab is to be reconstituted with 10ml SWFI
3. Send 0.9% normal saline bag with CADD HI-Volume administration set (reference: 21-7355-24) or Curlin HI-Volume administration set (reference: 3-13-810) which contain a low protein binding 0.2-micron air eliminating filter.
4. The Reservoir Volume for pump programming must be equal to the total volume
5. Please note these infusions will be pole-mounted so the need to purge air is not necessary.
6. All new patients will receive an infliximab placement (reference: 7-00-028) for guidance on home-mixing and administration
7. ANA Kit
   a. 2-Acetaminophen 325mg tablets
   b. 2-Diphenhydramine 25mg capsules
   c. Diphenhydramine 50mg/ml vial
   d. 3-Epinephrine 1mg/ml ampule
   e. 1-Methylprednisolone 125mg vial
   f. 0.9% Sodium Chloride 500ml
   g. 3-1ml TB syringes
   h. 3- filter needles
   i. 3-Monoject Safety needles
   j. 2- 3cc syringes with needle
   k. 10 alcohol swabs
   l. Gravity tubing

C. Storage and Handling

1. Store vials at 2 F - 8 C (36 F - 46 F)
2. Reconstituted product must be infused within 3 hours of preparation

3. Refer to specific product packing and prescribing information for storage, stability, and excursion information

D. Compatibility
   1. Stable in NS solution
   2. Do not infuse with other agents

VI. NURSING GUIDELINES

A. Procedures
   1. Patient Selection
      a. Adults
         1) Active ankylosing spondylitis;
         2) Moderately to severely active Crohn's disease with inadequate response to conventional therapy;
         3) Chronic severe plaque psoriasis as an alternative to other systemic therapy;
         4) Psoriatic arthritis;
         5) Moderately- to severely- active rheumatoid arthritis;
         6) Moderately- to severely active ulcerative colitis with inadequate response to conventional therapy.
      b. Children ≥ 6 years
         1) Moderately to severely active Crohn's disease with inadequate response to conventional therapy;
         2) Moderately to severely active ulcerative colitis with inadequate response to conventional therapy.
   2. Contraindications
      a. Hypersensitivity to infliximab, murine proteins or any component of the formulation; doses >5 mg/kg in patients with moderate or severe heart failure (NYHA Class III/IV)
      b. Canadian labeling: Additional contraindications (not in US labeling): Severe infections (eg. sepsis, abscesses, tuberculosis, and opportunistic infections); use in patients with moderate or severe heart failure (NYHA Class III/IV)

B. Compounding
   1. Reconstitute vials with 10 ml sterile water for injection. Swirl vial gently to dissolve powder. **DO NOT SHAKE**. Allow solution to stand for 5 mins.
   2. Draw up total dose and slowly inject into bag of 0.9% Sodium Chloride. The resulting infusion concentration should range between 0.4-4mg/mL
   3. Infusion of compounded dose should begin within 3 hours of preparation.

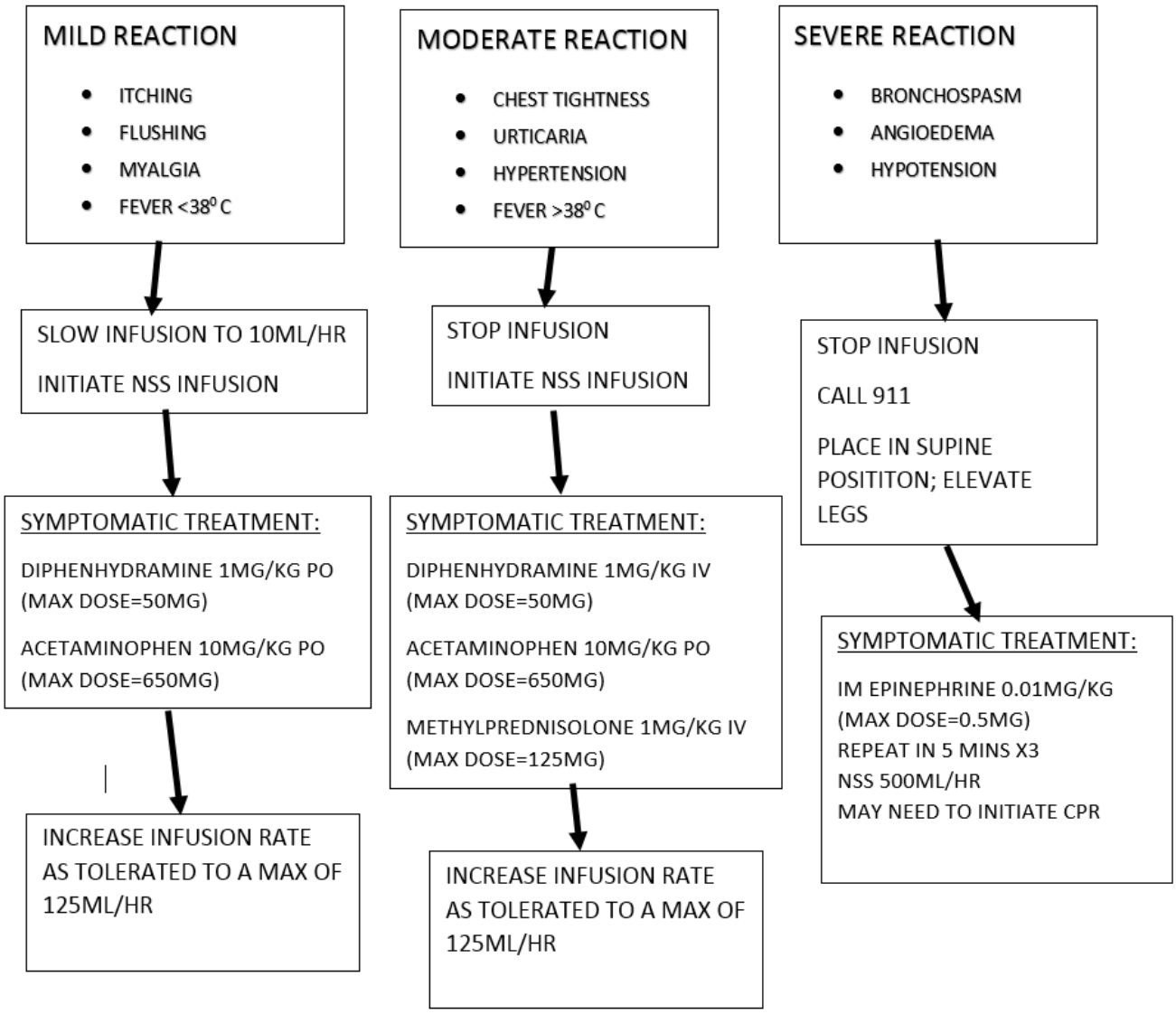
C. Infusion Rates
   1. Infusions will be administered continuously over two hours or per ordered titration unless previous infusion history dictates a slower rate.

2. Patients with established tolerance may be candidates for infusion times less than two hours. Appropriateness will be reviewed with the prescriber on a case-by-case basis.
3. Patients with history of severe infusion reactions should only be considered for home infusion after a thorough discussion of safety for the patient and risk vs. benefit with the physician. If home infusions continue, a slower infusion rate will be utilized.

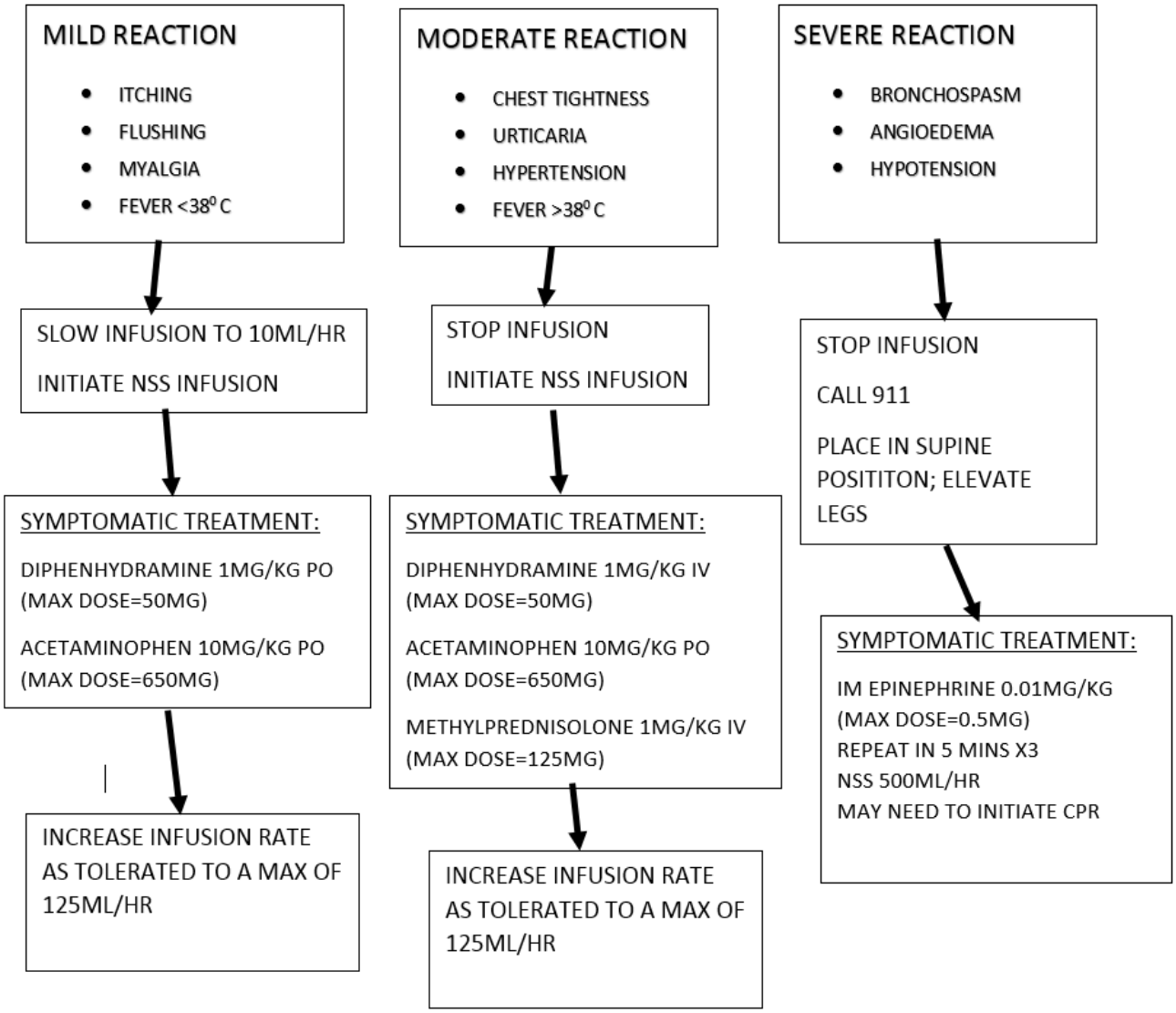
D. Clinical Monitoring
    1. Infusion reactions may occur. Premedication may be helpful.
    2. Treatment for hypersensitivity reactions should be available.
    3. Place and read PPD before initiation of therapy. Treatment of latent TB infection should be initiated prior to treatment with infliximab.
    4. Monitor for signs or symptoms of infection.
    5. Assess for signs of liver dysfunction
    6. Monitor labs throughout treatment.
    7. Do not use with live vaccines, such as BCG or influenza, or past allergies to mouse proteins.

E. Side Effects
    1. Headaches, GI upset, and Infections are among the most common side effects in patients.

APPENDIX 1: TREATMENT OF ADULT INFUSION REACTIONS



APPENDIX 1: TREATMENT OF PEDIATRIC INFUSION REACTIONS



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