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Protocol for Mucopolysaccharidosis type I (MPS I) Patients Started on Aldurazyme® (Laronidase)

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Protocol for Mucopolysaccharidosis type I (MPS I) patients started on Aldurazyme® (Laronidase):

Background:

Definition: Mucopolysaccharidosis type I (MPS I) is a rare, life-threatening autosomal recessive lysosomal storage disease with pathologic manifestations in most organ systems and tissues.

Causes: The disease is caused by a defect in the gene coding for the lysosomal enzyme α-L-iduronidase (IDUA); as a result, the cells of affected individuals are either unable to produce the enzyme or produce it in low amounts. This results in an inability of the lysosome to effect the stepwise degradation of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate, which are important constituents of the extracellular matrix, joint fluid, and connective tissue throughout the body.Because the disease is rare, and early symptoms can mimic other more common disorders, MPS I is often underrecognized and diagnostic delays are common.[1]

Classification:

- MPS I H (Hurler) syndrome
- MPS I H/S (Hurler-Scheie)
- MPS I S (Scheie) syndrome

All they shared the same genetic defect and biochemical abnormalities and differentiated phenotypically as Hurler syndrome represent the most sever phenotype with earlier age of onset while Scheie syndrome represent later age of onset and mildest phenotype and Hurler-Scheie in between the 2 spectrum.

Clinical features: The most severely affected patients at one end of the MPS I continuum are categorized as having the "Hurler" phenotype. These patients experience rapidly progressive disease manifestations beginning in infancy and are diagnosed at a median age of 0.8years.[2] Earliest symptoms include development of "coarse" facial features, corneal clouding, hepatomegaly, kyphosis, and inguinal and umbilical hernias. Later symptoms include dysostosis multiplex; severe arthropathy; impaired hearing, respiration, and cardiac function; and progressive mental impairment. Without treatment, pproximately 75% of patients with Hurler syndrome die before age 10, usually from obstructive airway disease, respiratory infections, and cardiac complications. Scheie syndrome represent later age of onset and mildest phenotype and Hurler-Scheie in between the 2 spectrum.[1-3]

Diagnosis: usually by findings of high dermatan and heparin sulfate in urine mucopolysaccharide analysis. The diagnosis is confirmed by deficiency of the enzyme on dry blood spot or white blood cell and DNA molecular testing of *IDUA* gene.[2]

Treatment: includes symptom-based interventions, enzyme replacement therapy with Aldurazyme® (laronidase) and hematopoietic stem cell transplantation (particularly very young, severely affected patients).[1-5]

Purpose: The purpose of this policy is to dictate the management of patients with Mucopolysaccharidosis type I (MPS I) who are eligible for enzyme replacement therapy.

Baseline assessments and investigations prior to initiation of enzyme replacement therapy(ERT):[6,7]

- Height, Weight, Head circumference
- Blood pressure
- Enzyme activity level
- DNA molecular testing for IDUA gene
- IgG antibody test
- CBC, diff
- Chem1
- Liver enzymes
- CPK level
- Bone profile and vitamin D levels
- Urine for mucopolysaccharides
- Urine analysis
- Neurology evaluation
- MRI of brain and spine
- Median nerve conduction velocity
- Cognitive testing (developmental quotient (DQ) or intelligence quotient (IQ)
- ENT evaluation (audiometry and ABR test)
- Ophthalmology evaluation(visual acuity, retinal examination, corneal examination)
- Respiratory evaluation (Chest X-ray, forced vital capacity, forced expiratory volume, sleep study)
- Cardiology evaluation (ECG, Echocardiogram)
- Skeletal survey
- Abdominal CT or MRI to determine the spleen and liver volume. If not available, then, abdominal ultrasound.
- Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life.

Enzyme replacement therapy(ERT) administration protocol:

Premedication (1 hour prior to ERT infusion) with:

- Acetaminophen (10-15 mg/kg) PO; _____ (mg) PO.
- Diphenhydramine (1mg/kg) IV; _____(mg) IV.
- Methylprednisolone (1mg/kg) IV; _____ (mg) IV.

➢ **Aldurazyme® (Laronidase)**[8-16]

- **Dose:** 0.58mg/kg (100unit/kg) IV once weekly.

- **Strength:** 5ml (2.9mg/5ml) = 500units/5mL, single use vial.
  Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example if the patient Weight 4 kg give 2.9mg (500unit) instead of 2.32mg (400unit).

- **Weight:** _____(kg): **calculated dose** _____(mg) IV.

- **Dilution:**
  - For patients ≤ 20 kg – dilute in 100 mL normal saline
  - For patients up to 30 kg with underlying cardiac or respiratory compromise – dilute in 100 mL normal saline.
  - For patients >20 kg – dilute in 250 mL normal saline

Special Precautions:

- **Stable only in Normal Saline.**
- The diluted Aldurazyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion rate:[15,16]

- The initial infusion rate of 2 U/kg/h may be incrementally increased every fifteen minutes, if tolerated, to a maximum of 43 U/kg/h. Therefore, you could apply the following regimens:

For less than or equal 20 kg:

Infusion rate	When to increase infusion rate to the next level
2 mL/hour for 15 minutes	If stable vital signs, increase the rate to …
4 mL/hour for 15 minutes	If stable vital signs, increase the rate to …
8 mL/hour for 15 minutes	If stable vital signs, increase the rate to …
16 mL/hour for 15 minutes	If stable vital signs, increase the rate to …
32 mL/hour for (~3 hours)	for remainder of infusion

The total volume of the administration should be delivered in approximately 3-4 hours.

For more than 20 kg:

Infusion rate	When to increase infusion rate to the next level
5 mL/hour for 15 minutes	If stable vital signs, increase the rate to …
10 mL/hour for 15 minutes	If stable vital signs, increase the rate to …
20 mL/hour for 15 minutes	If stable vital signs, increase the rate to …
40 mL/hour for 15 minutes	If stable vital signs, increase the rate to …
80 mL/hour for (~3 hours)	for remainder of infusion

The total volume of the administration should be delivered in approximately 3-4 hours.

Nurses: Monitor vital signs during (prior to each rate increase) and up to 1 hour following infusion. If abnormal, contact the physician to decrease the rate or temporarily hold the Aldurazyme® infusion.

Undesirable effects: The most commonly reported infusion reactions were pyrexia, chills, blood pressure increased, tachycardia, and oxygen saturation decreased. The most frequently occurring adverse reactions are rash, upper respiratory tract infection, injection site reaction, hyperreflexia, paresthesia, flushing, and poor venous access.

Less common but serious side effects: anaphylaxis and allergic reactions (during & up to 3 hours after infusion), risk of acute cardio-respiratory failure.

- **Note**:
  - If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion of Aldurazyme® and initiate appropriate medical treatment.
  - If an infusion reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms

Monitoring the response to enzyme replacement therapy:[6,7]

	Every 6 months	**Every 12 months**	**Every Other Year**
General			
Medical history **Physical examination** **General appearance**	**X**		
Lab test			
CBC, diff **Electrolytes** **Liver enzymes** **CPK level** **Bone profile and vitamin D levels**	**X**		
Neurology			
MRI of brain and spine			**X**
Median nerve conduction velocity			**X**
Cognitive testing (developmental quotient (DQ) or intelligence quotient (IQ)		**X**	
ENT evaluation (audiometry and ABR test)		**X**	
Ophthalmology evaluation(visual acuity, retinal examination, corneal examination)		**X**	
Respiratory evaluation (Chest X-ray, forced vital capacity, forced expiratory volume, sleep study)		**X**	
Cardiology evaluation (ECG, Echocardiogram)			**X**
Skeletal survey			**X**
Abdominal CT or MRI to determine the spleen and liver volume. If not available, then, abdominal ultrasound.			**X**
Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life.		**X**	

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