Canadian HPP Clinical Expert Committee

TERMS OF REFERENCE

1. PURPOSE

The Canadian HPP Clinical Expert Committee (Also known as the HPP Advisory Committee) has been established to provide expert advice on the treatment and management of Hypophosphatasia and the use of Strensiq® as a treatment option.

2. FUNCTIONS

The functions of the Canadian HPP Clinical Expert Committee are:

a) To provide advice on the current and emerging treatment options to health professionals with regards to HPP and to articulate the goals of treatment;
b) To advise on best practice (including timing of implementation and monitoring) for quality use of Strensiq®;
c) Manage the requests for Strensiq® review to the HPP Committee in a timely manner including
    i. Review the appropriateness and accuracy of diagnostic information
    ii Review applications for new patient starts
    iii Review requests for renewals of patients on Strensiq at 24 weeks, then at 48 weeks, then 1 year intervals to ensure that the patient is continuing to meet criteria for treatment
    iv. Develop guidelines for the initiation and discontinuation of Strensiq in patients with Perinatal HPP
d) Report to Provincial Health Authorities the recommendations of the committee;
e) Apprise the Provincial Health Authorities of issues arising from benefit reviews;

3. MEMBERSHIP

a) Chair:
The Committee will be chaired by 1 person, preferably a person with particular expertise in metabolic bone disease

The Chair is responsible for:
- Guiding the meetings according to the agenda and time available
- Ensuring all discussion items end with a decision, action or definite outcome
- Reviewing and approving the draft minutes before distribution
- Authoring correspondence external to the HPP Committee when a request for advice has been sought

NOTE: If an immediate decision is needed on urgent treatment of an unexpected severely affected neonate the Chair of the Committee or his/her replacement will be authorized to approve treatment for 1 month to allow time for full review by the Committee.

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b) **Secretariat:**
The secretariat for this committee will be Erika Bloomfield

The secretariat is responsible for:

- Scheduling meetings and notifying committee members
- Inviting specialists/subject experts to attend meetings when required by the committee
- Preparing agendas and issuing notices for meeting, and ensuring all necessary documents requiring discussion or comment are attached to the agenda
- Distributing the agenda and meeting materials
- Taking notes of proceedings and preparing minutes of meeting
- Distribute the minutes to all committee members. The minutes should be checked by the Chair and accepted by committee members as true and accurate record at the commencement of the next meeting.

c) **Membership:**
Membership of this Advisory Committee will be multi-disciplinary and include one member with special expertise in each of the core positions below:

- Genetics and Metabolism
- Neonatologist
- Endocrinologists (peds and adult)
- Pain Specialist
- Rheumatologist (peds and adult)

Committee members will cease to be a member of the HPP Advisory Committee if they:

- Resign from the committee
- Fail to attend 3 consecutive meetings
- Breach confidentiality

4. MEETING OPERATING PROCEDURES

a) **Accountability:**
The Committee is accountable to TBD (Provincial Drug Plans)

b) **Quorum:**
A quorum of the Advisory Committee shall be 50% of the Committee membership inclusive of the Chair and Secretary. Decisions will be made by

consensus. Where no consensus can be achieved, decisions will be made by voting.

c) **Meetings:**

There shall be a minimum of 4 meetings scheduled (quarterly) for a period of one (1) hour each calendar year. Additional meetings can be held at the call of the Chair through the secretary.

The agenda and accompanying materials shall be circulated within a minimum of seven (7) days prior to a meeting.

The business of the Committee may continue in its entirety with or without a full membership complement appointed.

Meetings will be held via Teleconference unless otherwise stated.

d) **Attendance:**

Attendance by the member at a minimum 60% of the meetings in a 12-month period is required. If a particular member's attendance is below the minimum, the Member's membership on the Committee may be reviewed at the discretion of the Chair, in consultation with the other members of the Committee.

e) **Term:**

Each member's participation on the Committee will be reviewed every 2 yrs.

f) **Voting:**

All decisions of the Committee will be by a majority vote, or in a manner as designated by the Committee. Each Committee member is allocated one vote irrespective of membership representation.

g) **Minutes:**

A master copy of the minutes will be located at the Children's Hospital Research Institute of Manitoba 5th floor (715 McDermot Ave Winnipeg, MB R3E 3P4). All members will be sent a copy of the minutes. An annual report will be prepared and distributed to all Committee members and Provincial Drug plans.

Canadian HPP Prescribing Guidelines Overview

Asfotase alfa Prescribing Criteria

For enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of perinatal, infantile, and childhood/juvenile-onset hypophosphatasia (HPP). Patients must have documented onset of signs/symptoms of HPP prior to 12 years of age. All requests for ERT with asfotase alfa (Strensiq®) should be first approved by the Canadian HPP Clinical Expert Committee. The province will send the HPP ERT Application Forms with their own complementary forms.

General Preamble

Confirmed diagnosis of perinatal/infantile or juvenile -onset hypophosphatasia (HPP) means:

- Confirmed diagnosis via genetic testing (documented tissue-nonspecific alkaline phosphatase (TNSALP) gene mutations(s) OR
- Serum alkaline phosphatase (ALP) level below the age and sex-adjusted normal range and plasma pyridoxal-5-phosphate (PLP) above the upper limit of normal AND
- Documented HPP- related skeletal abnormalities AND
- Patient is not an adult (18 years) at the time treatment is initiated AND
- Patient does not have odonto- or pseudo- HPP (i.e. craniosynostosis alone, premature loss of deciduous teeth alone and vitamin D deficiency to be ruled out) AND
- Management team/criteria in place that will follow recommendations re initiation, continuation and withdrawal of treatment in all patients approved for treatment including those with severe perinatal HPP

Patients should be initiated on treatment and followed in a specialized clinic with expertise in the diagnosis and management of HPP. Goals of therapy should be developed on a case-by-case basis prior to the initiation of therapy. For all patients with HPP, regardless of age at diagnosis, the pre-specified goals met at initiation of therapy should be reassessed following a trial of 24 weeks of therapy (24-48 weeks, in perinatal HPP); if Continuation Criteria are not met, the treatment should not be continued. ‘Withdrawal of treatment criteria’ yet to be developed.

Initiation Criteria – Perinatal/Infantile HPP:

- Assessed by a multidisciplinary management team who determines that the criteria noted above have been met as well as documented signs/symptoms that may include failure to thrive, poor growth, vomiting, hypercalcemia, B6-responsive seizures and/or respiratory failure with or without lung hypoplasia, and severe skeletal manifestations of HPP **(Neonatal HPP Management Guidelines)**
- Management team agrees to follow the Guidelines for Management of Severe Perinatal HPP **(Neonatal HPP Management Guidelines)**
- 24-48 week trial to be followed by reassessment by a metabolic specialist and multidisciplinary team, if applicable

Canadian HPP Prescribing Guidelines Overview

Initiation Criteria – Childhood HPP (after 6 months of age):

- Assessed by a metabolic specialist who determines that the criteria noted above have been met as well as documented signs/symptoms that include gait disturbance, rickets and RGIC score +/-Thacher score, bowing of legs, short stature unexplained by other reasons and, where applicable, pain scale score
- If treatment approved by HPP National Clinical Expert Committee recommends **beginning 24 week trial** , to be followed by reassessment by the referring metabolic specialist who issues report to HPP Clinical Expert committee providing the following information:
    - **24 week assessment** to determine response to treatment
        - Full clinical reassessment with weight, height, head circumference
            - Assess functional status with fait, muscle strength, mobility, pain, with repeat 6MWT and validated questionnaires ideally administered by physiotherapist
            - Quality of Life reassessment using validated questionnaire
            - Review medication history
        - BMI and nutritional health
        - Dental Health – teeth lost or gained
        - Radiographs to assess any healing of HPP skeletal abnormalities
        - Safety Monitoring- monitor, record and report any adverse effects including adverse skin reactions

Continuation Criteria after initial 24 week treatment trial completed:

- Additional 24 week trial (if recommended by Committee) is to be followed by reassessment by a metabolic specialist and further report to the Committee **as above** but in addition
    - Renal Ultrasound yearly
    - Ophthalmologic assessment yearly.
    - DEXA every 2 years
- Thereafter yearly follow-up reports with information as requested above are submitted to Canadian HPP Clinical Expert Committee for continued renewal of drug or reasons for withdrawal.

Winnipeg Regional Health Authority
Caring for Health
Office régional de la santé de Winnipeg
À l'écoute de notre santé

NEONATAL CLINICAL PRACTICE GUIDELINE	**Title:** **Hypophosphatasia in Newborns**	
	Approval Date: May 2018	**Pages:** *1 of 6*
	Approved by: Neonatal Patient Care Teams, HSC & SBH Child Health Standards Committee	**Supercedes:** *none*

1.0 PURPOSE AND INTENT

1.1 To describe the approach to the diagnosis and management for newborns with confirmed perinatal hypophosphatasia (HPP). HPP has been classified clinically according to age at first symptom onset, immediately after birth. This guideline focuses on the management of the most severe form, perinatal HPP. For cases where the diagnosis is made prenatally, this guideline can be used to inform the management team and family when developing a management plan. (See 4.3 in Decision-Making Structure).This guideline can also be used as a template for the management of infantile HPP with onset generally after the perinatal period but before 6 months of age.

2.0 PRACTICE OUTCOME

2.1 Newborns with perinatal hypophosphatasia receive the systemic support necessary to achieve the goals of treatment including: survival, enhanced respiratory function, improved bone mineralization, metabolic control, seizure control, prevention of renal failure, pain control, and improved growth and development.

3.0 DEFINITIONS

3.1 **Hypophosphatasia**: A rare inherited systemic, metabolic disorder caused by autosomal recessive mutations or a single dominant-negative mutation in the gene encoding tissue-non-specific alkaline phosphatase (TNSALP). It mainly affects bone and teeth mineralization. The perinatal form is at the most severe end of the spectrum of HPP and is evident either before birth on ultrasound or in the first few days of life. It is generally lethal without the pharmaceutical treatment with Asfotase alfa*.

3.2 **Asfotase alfa**: A human recombinant enzyme (TNSALP) replacement therapy (ERT) which replaces deficient TNSALP in patients with HPP.

3.3 **Abbreviations:**
ALP= alkaline phosphatase (also TNSALP)
PLP = pyridoxal 5 phosphate (also Vitamin B6)
PTH = parathyroid hormone
CBC = Complete Blood Count
BUN = blood urea nitrogen
PEA = phosphoethanolamine
Ca/Cr = calcium/creatinine ratio

4.0 GUIDELINES

4.1 Consult Medical Genetics Service and any other relevant medical subspecialties including Endocrinology, Respirology, Neurology, Neurosurgery and Orthopedics, as indicated.

4.1.1 Educate the multidisciplinary care team about the disease and treatment including potential complications and outcomes.

4.2 To confirm the diagnosis of HPP perform the following immediately after birth or as soon as diagnosis is suspected:

  4.2.1 Chest x-ray – generally performed as a result of need for respiratory support with the primary finding of a lack of appearance of mineralization in the ribs with or without lung hypoplasia.

  4.2.2 Skeletal x-ray survey – to confirm the findings and provide a baseline for later comparison. If baby cannot tolerate transport, perform a partial skeletal survey with portable equipment at the bedside, with x-ray of the long bones.

  4.2.3 Total serum ALP – to provide confirmation of the diagnosis of HPP. Low ALP differentiates it from osteogenesis imperfecta, campomelic dysplasia and other chondrodysplasias, as well as provides a baseline value.

  4.2.4 Other baseline laboratory testing: Plasma PLP (Vitamin B6), Ionized Calcium, Calcium, PTH, 25 Hydroxy Vitamin D, Phosphate, CBC, Liver Function, Electrolytes, Creatinine, BUN. Urine for PEA (if available), Urine Calcium, Urine Creatinine, Urine Ca/Cr ratio.

  4.2.5 Genetic testing (if not yet performed) – ALPL gene sequencing or direct mutation analysis.

Decision-Making Structure

4.3 When a diagnosis is suspected or confirmed by the Genetics/Metabolics team, discuss the diagnosis, natural history and outcome of perinatal HPP without ERT with the family and discuss the possibility of initiating ERT. For cases when the diagnosis is suspected or confirmed prenatally, develop a management team including Neonatology, Genetics and Maternal-Fetal Medicine to discuss diagnosis and develop a written detailed management plan including preterm induction of labour documenting the families wishes with respect to resuscitation. This is initiated by the Genetics/Metabolics team. Consider a consult to the Palliative Care/Symptom Management Team depending on parental direction.

4.4 The Genetics/Metabolics team with the healthcare team, review the baby (case) in order to quantify and predict treatment response and develop an individualized approach to potential treatment failure and criteria for recommendations for treatment continuation or withdrawal of care. Use clinical and radiological markers (eg degree of lung hypoplasia) as treatment response. Assess lung function and response using whatever techniques are available.

4.5 Plan team meetings to include the family on a regular basis (weekly or bi-weekly) to review treatment response and any decisions that need to be made. Utilize decision guides or consultants with the family if there is decision conflict. Consider the amount of information and questions asked to the family to avoid overwhelming them while continuing to ensure their full understanding.

Pharmacologic Treatment

4.6 After obtaining appropriate approvals initiate ERT with Asfotase alfa (Strensiq™) subcutaneous 2 mg/kg per dose given three times a week.

4.7 Rotate injection sites and monitor for injection site erythema, discoloration, pain, pruritis, swelling, induration, macule, bruising and nodules.

4.8 Increase the dose only under the direction of the Metabolic Genetics consulting physician.

Treatment Initiation Phase

4.9 Provide respiratory support to keep blood gases and oxygen saturations within the normal range providing ventilator support as required.

4.10 Establish central venous access and initiate total parenteral nutrition.

4.11 Insert an arterial line for blood sampling. Do not obtain blood for any purpose from capillary samples. Squeezing may result in fractures.

4.12 Initiate appropriate enteral nutrition and advance as tolerated. Follow serum calcium levels and adjust calcium intake accordingly.

4.13 Manage pain using opiodes and monitor effectiveness using a validated age appropriate pain scale.

4.14 Perform baseline evaluation including:
  4.14.1 Renal ultrasound- looking for nephrocalcinosis
  4.14.2 Eye exam – looking for ectopic calcification and increased intracranial pressure
  4.14.2 Hearing screening

4.15 Perform baseline respiratory and age-appropriate pulmonary function testing with ongoing frequency dependent based on individual patient presentation.

4.16 Monitor for seizures. Initiate treatment with Vitamin B6 and consult Neurology for ongoing management.

Treatment Monitoring Phase

4.17 Follow the frequency of management, investigations and review outlined below as a minimum and increase frequency as needed or indicated by clinical presentation and results.

4.18 Daily:
  4.18.1 Respiratory support needs.
  4.18.2 Sedation and analgesia requirements
  4.18.3 Infant’s tolerance of and response to handling as reported by bedside nurses.

4.19 Twice weekly:
  4.19.1 Laboratory investigations: Serum ionized calcium, phosphate, ALP & PTH
  4.19.2 Weight

4.20 Once a week:
  4.20.1 Head circumference and length
  4.20.2 Nutrition review
  4.20.3 Urine testing for calcium & creatinine
  4.20.4 Family and team meetings to review treatment course, evidence of response/non-response and drug dosing

4.21 Every two weeks:
  4.21.1 Chest x-ray.
  4.21.2 Pulmonary function testing (if available).

4.22 Once a month:
  4.22.1 Patient growth parameters including length/height, weight, body mass index, head circumference and shape routinely.
  4.22.2 Multidisciplinary meeting (with clinical consultants) to review treatment course and discuss unified recommendation regarding continuation of therapy.

4.23 Every 3 months:
  4.23.1 Radiologic testing of the chest, wrists and knees (skeletal survey) to monitor skeletal improvement. Do more frequent imaging dependent on disease severity. Minimize radiation exposure unless clinically indicated.

- 4.23.2 Serum for: ALP, Plasma PLP, Ionized Calcium, Calcium, 25OHVitamin D, Phosphate, CBC, Liver Function, Electrolytes, Creatinine, BUN.
- 4.23.3 Urine for: PEA (if available), Calcium, Creatinine.

4.24 Every 6 months:

- 4.24.1 Eye exam for increase intracranial pressure and calcium deposition.
- 4.24.2 Renal ultrasound for nephrocalcinosis.

4.25 As clinically indicated:

- 4.25.1 Standard-of-care investigations and treatment for seizures.
- 4.25.2 Standard of care investigations for nutrition and feeding status and consideration of gastrostomy tube insertion.
- 4.25.3 Craniofacial CT scan (low dose, bone only), to investigate for craniosynostosis and related complications.
- 4.25.4 Consultation with Bioethicist.

Note: See table in Appendix A for summary of baseline and ongoing laboratory testing.

Clinical Considerations

4.26 Respiratory management:

- 4.26.1 Assess the whole clinical presentation for decisions on increasing or decrease support as no one indication alone is an accurate reflection of the infant’s respiratory capability.
- 4.26.2 Change respiratory support settings in very small increments as each will have a bigger impact than expected.
- 4.26.3 Plan routine suctioning due to infant’s inability to take deep breaths. Assess need for adjustment as respiratory status indicates.
- 4.26.4 Consider alternate modes of ventilation both in escalating and de-escalating respiratory support as bone structure improves in order to minimize pulmonary impact of mechanical ventilation. (See guideline)

4.27 Cardiovascular management:

- 4.27.1 Establish and maintain central venous access. Peripheral intravenous starts are very difficult due to the lack of bone structure to stabilize. Utilize umbilical venous access for as long as possible in the newborn period and progress to surgical cutdown if necessary.
- 4.27.2 Monitor cardiovascular status using integrated evaluation of neonatal hemodynamics (IENH) and targeted neonatal echocardiography as indicated if available. (See guideline)
- 4.27.3 If chest compressions are required, depress sternum to $^{1}/_{3}$ of the anterior-posterior diameter of the chest, using only enough force to achieve this depth in order to prevent causing damage to the bones.

4.28 Positioning, handling and comfort:

- 4.28.1 Support baby on a high density foam mattress with only a single layer between the baby and the mattress to optimize pressure relief.
- 4.28.2 Move the baby as a single unit using a “turning sheet” in order to provide optimum support to the trunk and limbs. This is essentially a small sheet under the baby that is not tucked in at the ends, similar to a “slider”, to allow turning the baby without grasping the limbs or head.
- 4.28.3 Assess pain using a validated age-appropriate pain scale every 3-4 hours and to assess effectiveness of analgesia. (See guideline)
- 4.28.4 Provide ongoing analgesia and additional doses before significant position changes and as needed.
- 4.28.5 As comfort improves wean opiates gradually using a stepped approach and monitor for symptoms of withdrawal.

4.29 Skin management:
  4.29.1 Inspect the skin at all pressure points and under skin folds (axilla, neck, groin) for signs of erythema and skin breakdown.
  4.29.2 Prevent skin breakdown by maintaining an appropriate moisture balance using skin barrier products and/or appropriate lotions or other infant-appropriate skin products.

4.30 Parent participation in care:
  4.30.1 Provide opportunities for “modified” skin to skin contact with parents able to sit at baby’s level of the bed with arms placed gently across baby’s shoulders or around trunk and cradling baby’s head.
  4.30.2 Encourage parents to provide skin hygiene, oral care, diaper care and more as appropriate.
  4.30.3 As baby tolerates, have parents “hold” baby with baby supported on the bed’s memory foam mattress.
  4.30.4 Teach parents to do increased physical care including suctioning as appropriated.
  4.30.5 Continue to find ongoing new aspects of care that the parents can participate in.

5.0 REFERENCES

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6.0 PRIMARY AUTHORS

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6.2 Doris Sawatzky-Dickson, Neonatal Clinical Nurse Specialist

APPENDIX A

Routine Laboratory Testing in the first year of life

Note: minimum frequency – monitor more closely during acute illness as indicated by clinical status

Blood

Baseline	1 month	3 months	6 months	12 months
ALP		ALP	ALP	ALP
Plasma PLP	Plasma PLP	Plasma PLP	Plasma PLP	Plasma PLP
Ionized Calcium	Ionized Calcium	Ionized Calcium	Ionized Calcium	Ionized Calcium
Calcium	Calcium	Calcium		
PTH				
Vitamin D	Vitamin D	Vitamin D	Vitamin D	Vitamin D
Phosphate	Phosphate	Phosphate	Phosphate	Phosphate
CBC	CBC	CBC	CBC	CBC
Liver Function	Liver Function	Liver Function	Liver Function	Liver Function
Electrolytes	Electrolytes	Electrolytes	Electrolytes	Electrolytes
Creatinine	Creatinine	Creatinine	Creatinine	Creatinine
BUN	BUN	BUN	BUN	BUN

ALP= alkaline phosphatase; PLP = pyridoxal 5 phosphate; PTH = parathyroid hormone;
CBC = Complete Blood Count; BUN = blood urea nitrogen

Urine

Baseline	1 month	3 months	6 months	12 months
PEA (if available)	PEA (if available)	PEA (if available)	PEA (if available)	PEA (if available)
Calcium	Calcium	Calcium	Calcium	Calcium
Creatinine	Creatinine	Creatinine	Creatinine	Creatinine
Ca/Cr	Ca/Cr	Ca/Cr	Ca/Cr	Ca/Cr

PEA = phosphoethanolamine; Ca/Cr = calcium/creatinine ratio

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