ENDOCRINE SOCIETY PRESENTS

Diagnosis and Management of Hypophosphatasia: IMPROVING PATIENT OUTCOMES

SATURDAY, APRIL 1, 2017
7:00 – 9:30 PM
Registration & Meal Service:
6:30 – 7:00 PM
Hyatt Regency Orlando
Regency Ballroom R on the Convention Level

PROGRAM CHAIR
Leanne Ward, MD, FRCPC
Senior Scientist, CHEO Research Institute
Research Chair in Pediatric Bone Health, University of Ottawa
Associate Professor, Faculty of Medicine, University of Ottawa
Director, Pediatric Bone Health Clinical and Research Programs, CHEO

FACULTY
Erik Imel, MD, MS
Assistant Professor of Medicine and Pediatrics, Indiana University, School of Medicine
Linda DiMeglio, MD, MPH
Associate Professor of Pediatrics, Indiana University, School of Medicine

AGENDA
Alkaline Phosphatase in Health and Disease
Clinical Spectrum of Hypophosphatasia
Treatment Options in the Management of Hypophosphatasia

LEARNING OBJECTIVES
Upon completion of this educational activity, participants will be better able to:
• Describe the role of alkaline phosphatase and discuss the genetic underpinnings of hypophosphatasia
• Describe the skeletal and non-skeletal manifestations of hypophosphatasia
• Apply recently approved treatment option in perinatal, infantile and juvenile-onset hypophosphatasia
• Management of ongoing treatment of patients with hypophosphatasia

CME CREDITS: 2.5
AMA PRA Category 1 Credits™

This activity is supported by an educational grant from Alexion Pharmaceuticals, Inc

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ENDOCRINE SOCIETY
SYMPOSIUM AGENDA

Diagnosis and Management of Hypophosphatasia: Improving Patient Outcomes
Saturday, April 1, 2017

7:00 – 7:05 PM   Welcome and Introduction
                  Leanne Ward, MD, FRCPC

7:05 – 7:45 PM   Alkaline Phosphatase in Health and Disease
                  Erik A. Imel, MD

7:45 – 8:25 PM   Clinical Spectrum of Hypophosphatasia
                  Linda A. DiMeglio, MD, MPH

8:25 – 9:05 PM   Treatment Options in the Management of Hypophosphatasia
                  Leanne Ward, MD, FRCPC

9:05 – 9:10 PM   Summary
                  Leanne Ward, MD, FRCPC

9:10 – 9:30 AM   Audience Q&A

FACULTY

Leanne Ward, MD, FRCPC – Program Director
Associate Professor, Departments of Medicine and Surgery
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Medical Director, Pediatric Bone Health Clinical and Research Programs
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Associate Professor of Pediatrics
Director of Career Development and Co-Chair of the Pediatric Protocol Development Team
Indiana University Clinical and Translational Science Institute
Indianapolis IN
Leanne Ward, MD, FRCPC – Program Director
Dr. Leanne Ward is an Associate Professor of Pediatrics at the University of Ottawa where she has held a Research Chair in Pediatric Bone Health since 2010. She is the Medical Director of the Pediatric Bone Health Clinical and Research Programs at the Children’s Hospital of Eastern Ontario and a pediatric endocrinologist within the Division of Endocrinology and Metabolism. Dr. Ward’s research program is dedicated to the study of bone development and the treatment of bone disorders in children. She has been the principal investigator of the “STOPP” research program (STeroid-induced Osteoporosis in the Pediatric Population), a pan-Canadian project funded by the Canadian Institutes of Health Research to evaluate the effect of glucocorticoids on bone health in children with chronic illnesses. Dr. Ward actively leads and collaborates on a number of clinical trials for children with osteogenesis imperfecta, rickets and chronic illness osteoporosis. She has served as an endocrinology and bone health advisor to various national and international organizations on various aspects of skeletal health in children, including the Centres for Disease Control Clinical Care Guidelines for Duchenne Muscular Dystrophy and the International Conference on Children’s Bone Health. Dr. Ward has received a number of awards for her work in pediatric bone health, including a Canadian Child Health Clinician Scientist Career Development Award, a Canadian Institutes for Health Research New Investigator Award, a Canadian Child Health Clinician Scientist Career Enhancement Award, and two, five-year Research Chairs in Pediatric Bone Health (University of Ottawa, 2010 and 2015).

Erik A. Imel, MD, MS
Dr. Imel is an Associate Professor of Medicine and Pediatrics at the Indiana University School of Medicine and Riley Hospital for Children. He is Board Certified in both adult endocrinology and pediatric endocrinology. His clinical and research focus is in metabolic bone disorders in children and adults, especially rare bone disorders including disorders of phosphate metabolism.

Linda A. DiMeglio, MD, MPH
Dr. DiMeglio is a Professor in the Department of Pediatrics, Section of Pediatric and Diabetology at the Indiana University School of Medicine. After graduating from Harvard University with honors, Dr. DiMeglio obtained her MD from the University of Pennsylvania in Philadelphia, PA and performed her residency in Pediatrics at Children’s Memorial Hospital (Northwestern University) in Chicago, IL. She completed her fellowship in Pediatric Endocrinology and received her Master’s in Public Health from Indiana University-Purdue University, Indianapolis. Dr. DiMeglio has been working in clinical and translational research with a focus on novel technologies and therapies for type 1 diabetes and therapies for metabolic bone disease and since her fellowship. She performed the first randomized, controlled trial of insulin pump therapy for very young children and is currently the principal investigator for a multisite study designed to optimize the use of continuous glucose monitors in children with diabetes under the age of 8. She also is an active clinician, sees patients with endocrine disorders and diabetes in clinics and teaches medical students, residents, and fellows.
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The Endocrine Society is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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**LEARNING OBJECTIVES**

Upon completion of this educational activity, learners will be better able to:

- Describe the role of alkaline phosphatase and discuss the genetic underpinnings of hypophosphatasia
- Describe the skeletal and non-skeletal manifestations of hypophosphatasia
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- Management of ongoing treatment of patients with hypophosphatasia

**TARGET AUDIENCE**

This continuing medical education activity should be of substantial interest to endocrinologists and endocrine fellows, pediatric endocrinologists and pediatric endocrine fellows, and other healthcare professionals caring for patients with metabolic bone disorders.

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Linda A. DiMeglio, MD: Investigator, Alexion
Leanne Ward, MD: Advisory Group Member, Alexion; Investigator, Novartis Pharmaceuticals

The faculty reported the no relevant financial relationship: Erik A. Imel, MD

The following SPC member who reviewed content for this activity reported relevant financial relationships:

E Michael Lewiecki, MD: Consultant, Amgen, Merck, Eli Lilly, Radius Health, Shire, Abbvie and Alexion; Speaker, Alexion, Shire; Research Grant Support, Amgen, Eli Lilly, Merck

Joan Han, MD: Research Support, Rhythm Pharmaceutical

The following SPC Committee members reported financial relationships:

Zahid Ahmad, MD: Research Support, Regeneron, FH Foundation; Consultant, Regeneron; Speaker, Amgen, Genzyme, Sanofi

Andrew Ahmann, MD: Research Support, Dexcom, Lexicon, Medtronic, Novo Nordisk; Consultant, Dexcom, Novo Nordisk, Trividia Health

Giuseppe Barbesino, MD: Spouse, employee of Genzyme

John Carmichael, MD: Research Support, Novo Nordisk, Chiasma, Novartis, Pfizer, Strongbridge Biopharma; Speaker, Novartis; Advisory Board, Pfizer, Chiasma, Ionis Pharmaceuticals

Natalie Cusano, MD: Research Support, Shire; Speaker, Shire

Alan Kelly, MD: Speaker, Eli Lilly

Lisa Nachtigall, MD: Consultant, Ipsen, Novartis, Corcept; Grant Support/Investigator, Chiasma

Neda Rasouli, MD: Research Support, Novo Nordisk, Calibra, INTARCIA Therapeutics, GlaxoSmithKline, Bristol Meyer Squibb, AstraZeneca /Amylin, Ionis Pharmaceuticals, Boehringer Ingelheim

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Alkaline Phosphatase in Health and Disease

Erik Allen Imel, M.D.
Associate Professor of Medicine and Pediatrics
Endocrinology
Indiana University School of Medicine
April 1, 2017

Disclosures
• None
• No off-label medication discussions.

Objectives
• Review the role of alkaline phosphatase
  – Gene
  – Protein function and substrates
• Identify conditions associated with abnormal alkaline phosphatase levels
  – High
  – Low
• Identify consequences of low alkaline phosphatase
• Describe genetic abnormalities causing hypophosphatasia

Clinical case question
This 6 month old infant has seizures, hydrocephalus, nephrocalcinosis and rachitic changes. Which abnormality, if present, would differentiate her cause of rickets most specifically from other types of rickets?
A. Low serum phosphorus
B. High pyridoxal 5’-phosphate
C. Low serum calcium
D. Low urinary calcium
E. High bone specific alkaline phosphatase

Alkaline phosphatase gene and protein
• In humans 4 genes encode alkaline phosphatase
• 3 “Tissue-specific” ALPs on chromosome 2q34-37
  – Intestinal ALP
  – Placental ALP
  – Germ-cell placental-like ALP
• 1 “Tissue-nonspecific” ALP (TNSALP) expressed in liver, kidney, bone
  – encoded by the ALPL gene on 1p36.1-p34
  – >50kb, 12 exons, 11 translated
  – 507 amino acids
  – Tissue-specific glycosylation (Bone ALP has O-glycosylation)

Alkaline phosphatase enzyme function
• Works at physiologic pH
• Dimerizes
  – Each monomer binds 4 metal ions
  – 2 Zn, 1 Mg, 1 Ca
• An ectoenzyme
• Anchored to cell membranes or membrane vesicles by glycosyl phosphatidyl inositol (GPI)
• Also released into circulation

Image from Imel, in Pediatric Endo Board Review 2013, The Endocrine Society
Buchet et al. Methods Mol Biol 2013; 1053:27-51;
Whyte in Pediatric Bone, Second edition, Elsevier 2012
**ALP substrates**

- Dephosphorylates phosphoesters and inorganic pyrophosphate (PPI)
- ALP competitively inhibited by inorganic phosphate (Pi)

![Diagram](ALP_substrates.png)

**Intestinal ALP**

- Component of the gut mucosal defense
- Prevents bacterial invasion through gut mucosa
- Can detoxify endotoxin (LPS) by removing a Pi group
- In mice, different isoforms have different effects on fat absorption.

![Intestinal ALP](Intestinal_ALP.png)

**Intestinal ALP**

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![Intestinal ALP](Intestinal_ALP.png)

**Placental and Placental-like**

- Uncertain function
- May be expressed in some tumors.

![Placental and Placental-like](Placental_and_Placental-like.png)

**Kidney ALP**

- Present in kidney proximal tubule
- Regulates PPI metabolism
  - (though PPI is excreted primarily downstream of the proximal tubule)
- Can detoxify endotoxin (LPS) by removing a Pi group

![Kidney ALP](Kidney_ALP.png)

**Liver ALP**

- Expressed in hepatocytes and cholangiocytes and secreted into bile
- Inhibits ductal bile secretion
  - By decreasing activity of the basal CL-/HCO3- exchanger
- May act as ATPase and modulate purinergic signaling
- Dephosphorylates and inactivates CFTR
  - In experimental conditions
- Can detoxify endotoxin (LPS) by removing a Pi group

![Liver ALP](Liver_ALP.png)

**Bone ALP and PPI**

- Bone ALP is expressed in hypertrophic chondrocytes and osteoblasts.
- Hydroxyapatite (HA) crystals form in membrane vesicles and are propagated on the collagen matrix.

![Bone ALP and PPI](Bone_ALP_and_PPI.png)

**Bone ALP and PPI**

- Bone ALP cleaves PPI, releases Pi, and facilitates crystal growth.
  - Formation of HA
    - Optimal at Pi/PPI ratio >140
    - Inhibited at ratio <70
    - Calcium PPI dehydrate (CPPD) precipitates at ratio <6.
Bone ALP and PPI

• This process is also important for mineralization of teeth.
• Cementum and dentin are under mineralized in HPP.

Bone ALP and PPI

• ALP increases to minimize PPI and to optimize Pi at the mineralization front in:
  • Conditions of impaired mineral availability
    — Nutritional rickets
    — Hypophosphatemic rickets
    — Etc.
  • Increased bone formation
    — Physiologic (childhood and adolescence)
    — During stimulation by anabolic bone agents
    — Pathologic (Fibrous dysplasia, Pagets, etc.)
    — Etc.

Bone ALP, HPP and PPI

• Without ALP, PPI accumulates, binds hydroxyapatite
• Inhibits propagation of crystals.
• Hydroxyapatite formation within membrane vesicles seems relatively preserved.

Bone ALP, HPP and PPI

• Without ALP, mineralization is impaired
  • Disruption of the growth plate
  • Rickets and osteomalacia
  • Skeletal deformity
  • Accumulation of extracellular calcium and Pi
    — Levels often high normal or high
    — Hypercalcemia
    — Nephrocalcinosis
  • Amorphous calcium pyrophosphate deposition
    — Pseudogout
    — Pyrophosphate arthropathy
    — Chondrocalcinosis

Bone ALP in vessels

• PPI inhibits calcification in vessels.
• TNSALP overexpression in vascular smooth muscle causes calcification.

Pyridoxal 5’-phosphate (PLP)

• Major form of vitamin B6
• PLP cannot cross plasma membranes.
  — Must be dephosphorylated to pyridoxal by TNSALP
  — Then rephosphorylated intracellularly to PLP.
• Without TNSALP, extracellular PLP increases.
• HPP does not typically cause full B6 deficiency syndromes (dermatitis, stomatitis, neuritis, anemia).
**ALP is expressed in CNS**

- Intracellular synthesis of GABA, serotonin, etc.
- In the CNS, PLP is a cofactor for synthesis of certain neurotransmitters.
- However, in severe HPP:
  - Low intracellular PL and PLP
  - Seizures
  - Can suppress seizures by taking pyridoxal (PL), the hydrophobic form of B6

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**Phosphoethanolamine (PEA)**

- Part of the glycosyl phosphatidylinositol (GPI) protein anchor complex

- Re-chained glycans

- GPI anchor structure

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**Phosphoethanolamine (PEA)**

- The specific source of high circulating PEA is uncertain in HPP
  - PEA may come from degrading these protein anchor complexes
  - Impaired breakdown by liver
  - TNSALP may breakdown PEA
  - PLP is a cofactor for O-PEA-phospho-lyase:
    - Converts PEA to acetaldehyde, Pi, and NH₃

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**Alkaline phosphatase measurement**

- The total alkaline phosphatase assay measures enzyme activity.
- Colorimetric substrates at a non-physiologic high pH
- Detects all ALP forms in serum
- Cannot be measured accurately in EDTA-plasma, (binds divalent cations)

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**Total ALP normal range varies with age, sex and laboratory**

- Many labs only give adult ranges.
- Know if your laboratory is giving you appropriate normal values.
- Inappropriate normal ranges lead to misdiagnosing conditions of high or low alkaline phosphatase.
Alkaline phosphatase isoenzyme assay

• Measure enzyme activity with and without heating > 65°C
  – Placental and placental-like ALP
  – Intestinal ALP
  – Liver ALP
  – Bone
• Reported as % of total ALP

Bone ALP

Direct bone specific alkaline phosphatase immunoassay

High alkaline phosphatase

• Rickets/osteomalacia
  – Vitamin D deficiency
  – Hypophosphatemic
  – Calcium deficiency
  – Other vitamin D related defects
• Hyperparathyroidism
• Pagets disease of bone
• Fibrous dysplasia of bone
• Transient hypophosphatasemia
• Biliary disease
• Some cancers
• Others

Source of high ALP?

• Clinical signs of rickets or bone disease
• Other biochemical markers of mineral metabolism
• Plain radiographs for rickets or bone lesions?

Low alkaline phosphatase

• Lab artifact (EDTA, citrate, oxalate tubes)
• Bone disorders
  – Hypophosphatasia
  – Cleidocranial dysplasia
  – Osteogenesis imperfecta
  – Adynamic renal osteodystrophy
• Endocrine issues
  – Hypothyroidism
  – Glucocorticoid excess
• Deficiencies
  – Vitamin C
  – Vitamin B12 / pernicious anemia
  – Zinc
  – Magnesium
  – Celiac disease
  – Starvation
• Toxicities
  – Vitamin D toxicity
  – Milk Alkali syndrome
  – Copper (Wilson's disease)
  – Heavy metal
• Medications
  – Clofibrate
  – Glucocorticoids
  – Antiresorptives
• Other:
  – Cardiac bypass surgery
  – Trauma, surgery
  – Massive transfusion
  – Multiple myeloma
  – Some cancers and chemotherapy

Reason for low ALP?

• Most of these are identifiable from the clinical picture
• Review medications, history
• However may require testing for other causes:
  – Creatinine
  – Zinc, Magnesium, Copper
  – Vitamin C, D, B12
  – Endocrine abnormalities
• If suspect HPP:
  – Check Bone ALP, PEA, PLP
  – Other biochemical markers of mineral metabolism

### ALP substrates

- PPI
- PLP
- PEA
- LPS
- ATP
- Others?

### PLP and PEA
- PLP levels are sensitive and specific to HPP
- Vitamin B6 supplement falsely elevates level

### Serum total alkaline phosphatase in HPP

### Hypophosphatasia

Consequences of HPP vary by severity of the enzyme defect:
- Odonto
- Adult
- Child
- Infantile
- Perinatal

More severe enzyme dysfunction

### HPP effects

**Skeletal**
- Demineralized skeleton
- Rachitic changes at growth plate
- Fractures
- Wide-appearing sutures due to ossification defect, but premature fusion
- Functional craniosynostosis, increased intracranial pressure
- Premature deciduous tooth loss, defective cementum

**Non-skeletal**
- Hypercalcemia, hyperphosphatemia
- Hyperammonemia
- Nephrocalcinosis
- Calcium pyrophosphate arthropathy, ossification of ligaments
- Muscle weakness, delayed motor milestones, poor feeding
- Seizures

### HPP Genetics

- 1:300,000 in Europe
- 1:100,000 in Canada
- 1:2500 in Mennonites from Manitoba, Canada
- Rare, but described in African ancestry
- More moderate or mild forms may be more common (up to 1:6000).
- The more severe forms (perinatal, infantile) are autosomal recessive.
- The milder forms can be autosomal recessive or dominant.
HPP Genetics

- >330 different disease-causing mutations reported
  - 71% Missense
  - 3% Large deletions
  - 13% Small deletions
  - 6% Splice site
  - 5% Nonsense mutations
  - 3% Small insertions
  - 1% Other
- New mutations continue to be reported

Mutation effects vary:
- Inactivate the enzyme
- Cause intracellular accumulation
- Low protein expression
- Dominant negative effects on the dimer

Mutation database:
- [http://www.sesep.uvsq.fr/03_hypo_mutations.php](http://www.sesep.uvsq.fr/03_hypo_mutations.php)
- Curated by Etienne Mornet at the Universite de Versailles

Clinical case question

This 6 month old infant has seizures, hydrocephalus, nephrocalcinosis and rachitic changes.
Which abnormality, if present, would differentiate her cause of rickets most specifically from other types of rickets?

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C. Low serum calcium
D. Low urinary calcium
E. High bone specific alkaline phosphatase

Summary

- ALP removes Pi groups from multiple substrates including
  - ATP, LPS, PPI, PEA, PLP
- ALP facilitates mineralization by decreasing local concentrations of the mineralization inhibitor PPI.
- ALP level (whether high or low) is an important marker for multiple diseases.
- Recognizing the forms of ALP and the clinical conditions leading to high or low ALP levels will facilitate appropriate further testing and diagnosis.

Thank you!
Clinical Spectrum of Hypophosphatasia

Linda A. DiMeglio, MD, MPH
Clinical Spectrum of Hypophosphatasia

Linda A. DiMeglio MD, MPH
Professor of Pediatrics

Objectives
• Describe different HPP presentations, including key laboratory findings
• Contrast HPP presentation with other metabolic bone disorders

Milestones in Hypophosphatasia (HPP)
• 1907 Suzuki et al. describe phosphatase enzyme
• 1923 Robinson and Soames describe “bone phosphatase”
• 1948 Hypophosphatasia identified as a syndrome
• 1955 Increased urinary phosphoethanolamine (PEA) described in HPP
• 1965 Increased pyrophosphate (PPi) described in HPP
• 1985 Increased pyridoxal 5’-phosphate (PLP)
• 1988 First TNSALP mutations causing HPP identified
• 1990s Mouse models for HPP developed
• 2012 First publication of successful enzyme replacement therapy in HPP
• 2015 Asfotase alfa therapy approved by multiple regulatory bodies

Clinical Spectrum
• Can present at all ages
• Highly variable among patients, even with same mutation(s)
Perinatal Hypophosphatasia

• Manifests in utero or at birth
• Severe hypo-mineralization of the skeleton and/or rachitic changes
• Fractures are often present
• Craniosynostosis
• Hypoplastic lungs and respiratory compromise
• Shortened limbs
• Babies or stillborn or die in the neonatal period

Perinatal “Benign” Hypophosphatasia

• Detected in utero by ultrasound or at birth
• Similar presentation to the perinatal form, but slowly improves and evolves into a milder form of the disease

Case #1: Presentation

• Normal growth and development until 4 months of age – noted to have hydrocephalus, shunt placed
• At 6 months of age – noted to have difficulty feeding, growth failure
• Work-up done: nephrocalcinosis with elevated serum creatinine
  • Creatinine increased gradually
• At 8 months of age, noted to have hypercalcemia
  • Endocrine consulted, treated with pamidronate...

Case #1

• Developed respiratory problems requiring tracheostomy and mechanical ventilation by 1 year of age.

INFANTILE HYPOPHOSPHATASIA: A CASE!

Now to...

Then

• Low alk phos (< 5 U/L) noted
• Bone isoform undetectable
• Serum pyridoxal phosphate and urinary pyrophosphate markedly elevated
Genetic analysis

- mutation in one TNSALP allele (stop codon); sequencing of exons showed no other mutations
- second allele either deleted or has a mutation in intron or upstream promoter sequence.

HPP: Systemic Manifestations

Presentation: Skeletal

- Osteoporosis/osteopenia
- Rickets/Osteomalacia
- Fractures
  - Can be low-trauma
  - Can be recurrent
  - Can be slow to heal
- Bone pain

- Poor Growth
- Craniosynostosis
- Chronic bone inflammation
Presentation: Dental
- Premature loss of teeth
  - With tooth root still attached
- Poor dentition
- Periodontal disease

Presentation: Respiratory
- Respiratory insufficiency/failure

Presentation: Renal
- Nephrocalcinosis
- Hypercalciuria

Presentation: Musculoskeletal
- Weakness
- Low tone
- Proximal myopathy
- Delayed motor milestones in infants
- Muscle Pain
- Immobility requiring wheelchair/other support

Presentation: Rheumatologic
- Chondrocalcinosis
- Pseudogout
- Calcium pyrophosphate dihydrate deposition
- Calcific Periarthritis
- Joint pain

Infantile Hypophosphatasia

Whyte NEJM 2012
Presentation: Neurologic

- Seizures
  - Due to PLP deficiency
  - B6 responsive
  - Increased intracranial pressure

In HPP

[Chemical reaction diagram]

H2PO4H2C

Alkaline phosphatase

Pyridoxal 5'-phosphate (PLP)

Pyridoxal (PL)

Vitamin B6 Deficiency and Seizures

Hypophosphatasia

Significant variability in clinical manifestations

- Early deciduous tooth loss – root intact
  - Enlarged pulp chambers noted on dental films
- Delayed motor milestones
- Static myopathy with gait disturbance
- Rachitic changes (wrists, ankles, ribs)
  - Valgus or varus LE deformity

Childhood Hypophosphatasia

Childhood HPP

Picture courtesy of P. Tebben
Adult Hypophosphatasia

- Frequently recognized in middle age
- Musculoskeletal complaints most frequent presenting symptoms
- Fractures
  - Recurrent, poorly healing metatarsal fractures
  - Sub-trochanteric femoral fractures
- May lose teeth prematurely
- Can have pseudogout
- Some with history of rickets/early deciduous tooth loss as a child

Adult Hypophosphatasia: Presentations

- Age at dx – 49 years (Range 35 – 73)
  - Age at onset of symptoms – 44 (30 – 72)
- Features:
  - Musculoskeletal pain - 41%
  - Fracture - 18%
    - Any history of fracture – 54%
    - Hip/femur fx – 23%
  - Chondrocalcinosis – 27%
  - Pseudogout – 14%

Case #2

4 year old boy referred by dentist because of early deciduous tooth loss.
- Central mandibular incisor lost at 2.5 years old
- Bilateral maxillary central incisors lost at age 4

- History
  - No fractures
  - No reported weakness or limb deformities
  - No seizures
Case 2

Labs

<table>
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<tr>
<th></th>
<th>Case 1</th>
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</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.8</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.5</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.6</td>
</tr>
<tr>
<td>25 OHD (ng/mL)</td>
<td>45</td>
</tr>
<tr>
<td>Alkaline Phosphatase (U/L)</td>
<td>55</td>
</tr>
</tbody>
</table>

Note: Alk Phos normal range given as 45-110

Odontohypophosphatasia

- Only childhood manifestation is early deciduous tooth loss
- Some may have Adult HPP but have not yet manifest additional features

4 Steps to Diagnosis

1) Consistent clinical features
2) Low serum alkaline phosphatase
3) Elevated plasma PLP and/or urine PEA
4) Genetic testing

Low alkaline phosphatase

- Lab artifact (EDTA, citrate, oxalate tubes)
- Bone disorders
  - Hypophosphatasia
  - Cleidocranial dysplasia
  - Osteogenesis imperfecta type II
  - Adynamic renal osteodystrophy
- Endocrine issues
  - Hypothyroidism
  - Glucocorticoid excess
- Deficiencies
  - Vitamin C
  - Vitamin B12 (pernicious anemia)
  - Zinc
  - Magnesium
  - Calcium disease
  - Starvation
- Medications
  - Clofibrate
  - Glucocorticoids
  - Antiresorptives
- Other:
  - Cardiac bypass surgery
  - Trauma surgery
  - Massive transfusion
  - Multiple myeloma
  - Some cancers and chemotherapy

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Other:

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- Some cancers and chemotherapy

Toxicities

Vitamin D toxicity
Milk Alkali syndrome
Copper (Wilson’s disease)
Heavy metal

Whyte in Pediatric Bone, Second edition
Elsevier 2012; McKiernan et al. JBMR 2014;29(7):1651

Deficiencies

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- Vitamin B12 (pernicious anemia)
- Zinc
- Magnesium
- Calcium disease
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Other:

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Toxicities

- Vitamin D toxicity
- Milk Alkali syndrome
- Copper (Wilson’s disease)
- Heavy metal
HPP Imposters

**Dental Abnormalities**
- HPP – Early deciduous tooth loss with root intact
- Osteogenesis Imperfecta – Dentinogenesis imperfecta
- X-linked hypophosphatemic rickets – Abscessed teeth

**Radiologic HPP Imposters**

<table>
<thead>
<tr>
<th></th>
<th>HPP</th>
<th>Nutritional Rickets</th>
<th>Hypophosphatemic Rickets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline Phosphatase</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

**Summary**

- HPP can present at a variety of ages with a wide range of clinical findings
- Laboratory hallmark is low serum alkaline phosphatase
  - Differentiates disease from other metabolic/genetic bone disorders

**Questions?**
Treatment Options in the
Management of Hypophosphatasia

Leanne Ward, MD, FRCPC
Objectives

• To discuss the treatment options for patients with HPP, spanning:
  – Supportive therapy
    • Multi-disciplinary
  – Bone-honing enzyme replacement therapy
    • Asfotase alfa
  – Therapy to increase production of ALP
    • PTH
    • Anti-sclerostin antibody
    • Bone marrow and mesenchymal stem cell transplant
  – Therapy to increase bone mass
    • Bisphosphonates

Supportive Therapy for the Systemic Manifestations of Low TNSALP Activity

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Infantile HPP</th>
<th>Benign prenatal</th>
<th>Odonto-HPP</th>
<th>Perinatal</th>
<th>Childhood</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowing of long bones</td>
<td>59</td>
<td>53</td>
<td></td>
<td>34</td>
<td>47</td>
<td>41</td>
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<tr>
<td>Gait disturbance</td>
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<td>53</td>
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<td>34</td>
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<td>41</td>
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<tr>
<td>Arthralgia</td>
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<td>53</td>
<td>50</td>
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<td>Bone pain</td>
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<td>Muscle weakness limiting daily activities</td>
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</tr>
</tbody>
</table>

Juvenile Onset HPP Patients Experience Significant Morbidity

- Non–pharmacological interventions: 94%
  - Surgical or medical intervention: 88%
  - Physiotherapy: 34%
  - Occupational therapy: 31%
- Mobility aids
  - Orthotics: 31%
  - Walking aids: 9%
  - Wheelchairs: 6%

**Supportive HPP Management**

<table>
<thead>
<tr>
<th>Medical Care</th>
<th>Surgery and Rehabilitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatology</td>
<td>Orthopedics</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>Neurosurgery</td>
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<td>Dentistry</td>
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<td>Occupational therapy</td>
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<td>Rheumatology</td>
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<tr>
<td>Nephrology</td>
<td></td>
</tr>
<tr>
<td>Genetics</td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td></td>
</tr>
</tbody>
</table>

**Supportive HPP Management: Mineral Ion Metabolism**

- **Hypercalcemia/hypercalcuria**
  - Calcium supplementation avoided
  - Loop diuretics, hyperhydration, steroids
- **Hyperphosphatemia**
  - Pi competitively restricts TNSALP activity and gene expression
  - Dietary phosphate restriction
  - Phosphate binders

**Overall Management**

*As with any complex disorder involving multiple services, a clinician from one of the sub-specialties needs to provide overall leadership, coordination and patient care advocacy.*

**Mineral Ion Metabolism with ERT**

- **Pre-ERT**
  - Hypercalcemia and hyperphosphatemia
- **Post-ERT**
  - Hungry bones syndrome!

**Patient Support Groups**

- Soft Bones Canada
- Soft Bones Foundation (U.S.)
- HPP-Choose Hope (U.S.)
- Hypophosphatasie Europe (France)
- Hypophosphatasie Deutschland (Germany)
- HypoPhosPhatasia Support Association of Japan (HPPSA-J)

**Vitamin D Status**

- **Vitamin D Insufficiency**
  - Should be treated but not zealously
- **Severe vitamin D deficiency**
  - $\uparrow$ PTH
- **Pre-ERT**:
  - Avoid high dose vitamin D therapy
  - Avoid vitamin D analogues

- **Treat to normalize PTH**
  - 25OHD level 20 ng/mL or 50 nmol/L
**Nutrition**
- Failure to thrive is a key presenting feature in the infantile and juvenile forms
- Support from a dietician
- Enteral and parenteral nutrition may be required
  - May develop oral aversions over time
- Anti-reflux therapy is often needed

**Pain and Physical Activity**
- **Pain:**
  - Anti-inflammatories are the mainstay of therapy
  - Psychological support and chronic pain management services
- **Physical activity/mobility:**
  - Muscle weakness++ and pain limit mobility
  - Exercise
  - Physiotherapy and assistive aids may be required
    - Orthotics
    - Walking aids
    - Wheelchairs

**Dental Care**
- **Early intervention:**
  - Optimal oral hygiene and regular dental care
  - Dental prosthetics in adults

**Neurological Management**
- **Seizures:**
  - B6-dependent seizures may be a presenting sign = a severe phenotype and poor prognosis
  - Treat with a **dephosphorylated form** of B6
- **Craniosynostosis:**
  - Neurosurgical release for patients with:
  - Raised intra-cranial pressure, Chiari malformation, hydrosyringomyelia

**Orthopedic Issues**
- **Scoliosis**
- **Osteochondral spurs, syndesmophytes**
- **Limb deformity**
- Fracture and “pseudo-fracture” management
  - Prolonged casting due to delayed healing
  - Stabilization of long bones with intra-medullary rods

**Objectives**
- To discuss the treatment options for patients with HPP, spanning:
  - Supportive therapy
    - Multi-disciplinary
  - **Bone-honing enzyme replacement therapy**
    - **Asfotase alfa**
  - Therapy to increase production of ALP
    - PTH
    - Anti-sclerostin antibody
    - Bone marrow and mesenchymal stem cell transplant
  - Therapy to increase bone mass
    - Bisphosphonates
Enzyme Replacement

• Infusions of plasma-enriched soluble ALP
  – ALP in the circulation
  – Unsuccessful

• TNSALP needs to be within the skeletal and cartilage matrices, in order to mineralize bone and growth plate

• Recombinant “fusion protein”
  – TNSALP ectodomain plus a deca-aspartate motif for bone targeting

Asfotase alfa

• Human recombinant TNSALP
• First-in-class, bone-targeted enzyme replacement therapy for treatment of HPP
• Fusion protein
  – TNSALP ectodomain
  – IgG1 Fc domain
  – Deca-aspartate
  • Bone-targeting motif

• Routes of administration:
  – SC injection
  – IV

Asfotase Alfa

Dramatically improved survival
Absence of dental disease, skeletal manifestations or seizures

Asfotase Alfa in the Treatment of Severe Infantile Onset HPP

• Ongoing Phase II, multinational, multicenter, open-label study
• Ten study sites: USA (6), UK (2), Canada (1), United Arab Emirates (1)

Initial Phase
Single IV (2.0 mg/kg)
1.0 mg/kg 3x wk SC

Extension Phase
(On-going)
Starting dose = final dose of initial phase

Whyte et al, NEJM, 2012;366::904-913;  Whyte et al, JCEM, 2016
Open-Label Study

- 11 children with life-threatening, perinatal or infantile hypophosphatasia
  - Diagnosis before 6 months of age
  - Age range 1 to 33 months
  - 6 required respiratory support
    - CPAP, O2, tracheostomy and ventilation
    - 4 had respiratory deterioration leading up to treatment
    - 7 tube-fed
    - One baby was on ambient air and fed orally (moderate)
- Observational – no statistical comparisons
- Asfotase 40 mg/ml
  - IV infusion 2 mg/kg
  - 1-3 mg/kg sc 3 times per week

Summary of Results

- Circulating TNSALP substrates diminished
- Increases in PTH as calcium dropped
  - No hypocalcemia, ectopic calcification
- Growth plate healing and skeletal densification
- Pulmonary function improved
- Improved developmental milestones
- Deciduous teeth erupted in all patients
  - No obvious impact on craniosynostosis

Primary Endpoint: Improved Bone Mineralization (RGI-C) at 6 Months in Patients Treated With Asfotase Alfa

- Significant improvement was noted as early as Month 3, continued, and was sustained through 3 years

Extensive hypomineralization in a 3 week old baby with hypophosphatasia

Improved mineralization after 24 weeks of Asfotase

18 month old baby with hypophosphatasia

Withdrew from the study after the initial IV infusion of Asfotase alfa
  - Fever, O2 desaturation, rigors and irritability with the infusion
  - Radiographs 14 months later shows substantial deterioration

Whyte et al, NEJM, 2012;366::904-913
Upon Arrival

Slide compliments Dr. Cheryl Greenberg

Baseline and 12 weeks following Asfotase alfa therapy

Slide compliments Dr. Cheryl Greenberg

Adverse Events

- No serious adverse events that were considered definitely drug-related
- One patient died from sepsis, after 7.5 months of therapy
- One patient withdrew consent after first infusion

Survival at one year:
95% of the treated group, 42% of historical controls

Survival at 5 years:
84% of the treated group, 27% of controls

Asfotase Alfa Treatment Improves Survival for Perinatal and Infantile Hypophosphatasia

Michael P. Whyte, Cheryl Rockman-Greenberg, Keichi Ozono, Richard Rine, Scott Moseley, Agustin Melian, David D. Thompson, Nicholas Bishop, and Christine Hofmann

(U Clin Endocrinol Metab 101: 334-342, 2016)

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Survival at 5 years:
84% of the treated group, 27% of controls

**5% of the ventilated controls survived, compared to 76% of the ventilated treated patients
Asfotase alfa therapy for children with hypophosphatasia


Asfotase Alfa for the Treatment of Juvenile HPP
Children 6 to 12 years of age

- Phase II, open-label, 2 sites (US, Canada); N = 12

**Initial Phase**
(n=13)
Randomized:
6 mg/kg/week (n=6)
9 mg/kg/week (n=7)

**Extension Phase**
(n=12)
Initial dose: 3 mg/kg/week
Increased to 6 mg/kg/week via protocol amendment

**Historical Control**
(n=16)
1 patient withdrew
12 patients continue treatment

BL 6 12 24 36*
Treatment (Months)

*1 mo. treatment; elective surgery

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Metaphyseal Splaying
Clinically can see improvement

4 years before treatment  2.5 years before treatment  6 months before treatment  6 months of treatment  4.5 years of treatment

Treatment start

Slide compliments Dr. Cheryl Greenberg

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>Asfotase Alfa (n = 13)</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>250</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Erythema</td>
<td>71</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td>26</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Intermittent</td>
<td>23</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Pain</td>
<td>18</td>
<td>6 (46)</td>
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<td>Atrophy</td>
<td>13</td>
<td>5 (38)</td>
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<td>Discoloration</td>
<td>17</td>
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<td>Induration</td>
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<td>Nodule</td>
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<td>1 (8)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

Table 2. Injection-site reactions

Height Z-score difference: 0.9
BMI Z-score difference: 0.5

Improved anthropometry
during Asfotase alfa treatment in juvenile HP

Safety results – injection site reactions

Erythematous reaction
First months of injections, disappears

Purple discoloration
Appears later, persistent

Abdominal lipohypertrophy
4 years

Objectives

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    • PTH
    • Anti-sclerostin antibody
    • Bone marrow and mesenchymal stem cell transplant
  – Therapy to increase bone mass
    • Bisphosphonates

Functional Outcomes
Mobility
6 Minute Walk Test

Strength and Agility
BOT-2 Score

Disability
CHAQ Test
**Parathyroid Hormone**

- PTH stimulates synthesis of TNSALP by osteoblasts
- Not an option in children
- Adult Study Outcomes: BMD, pain, mobility, biochemistry, skeletal radiography, bone histology
- Case reports with inconsistent effects, including initial but lack of sustained benefit


**Objectives**

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    - PTH
  - Anti-sclerostin antibody
  - Bone marrow and mesenchymal stem cell transplant
  - Therapy to increase bone mass
  - Bisphosphonates

**Anti-Sclerostin Antibody**

- IPSH244, an anti-sclerostin monoclonal antibody, improves disease biomarkers and markers of bone formation in patients with adult-onset hypophosphatasia (HPP)


**Bisphosphonate Therapy**

- Bisphosphonates do not rescue the phenotype in severe cases
  - Theoretically contraindicated
    - Analogues of inorganic pyrophosphate (PPI)
    - Mineralization inhibitors
    - No convincing benefit in adults
  - Could they play a role in decreasing fractures in children with milder forms of HPP?
  - Are there differences in the response to bisphosphonates in children compared to adults that need to be considered?

**Bone Marrow and Mesenchymal Cell Transplant**

- Tried with some success in severe forms
- High risk procedure, limited by pulmonary hypoplasia
- Case reports:
  - 5 patients, severe HPP
  - None died, all with degrees of improvement
  - One patient developed Ph+ leukemia


**Hypophosphatasia: Enzyme Replacement Therapy Brings New Opportunities and New Challenges**

Michael P Whyte
Department of Internal Medicine, Division of Bone and Mineral Diseases, Washington University School of Medicine, and Center for Metabolic Bone Disease and Molecular Research, Children’s Hospital of St. Louis, MO, USA

![Image of a pelvic X-ray showing a fracture in the right femur.]
**Effects of Pamidronate on Bone Tissue: Histomorphometric Analysis of Iliac Bone**

- *Iliac Biopsy*

<table>
<thead>
<tr>
<th>Without treatment</th>
<th>With treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone added by osteoblasts</td>
<td>Bone added by osteoblasts</td>
</tr>
<tr>
<td>Bone removed by osteoclasts</td>
<td>Bone NOT removed by osteoclasts</td>
</tr>
</tbody>
</table>

Rauch & Glorieux, Lancet 2004

---

**Bisphosphonate Therapy**

- Increases in cortical thickness are expected to occur in any bisphosphonate-treated patient who is growing
- Whether positive effects of newer generation bisphosphonates on *cortical bone modeling* provide an anti-fracture effect in milder forms has not been formally studied

---

**Summary and Conclusions**

- *Multi-disciplinary supportive care* remains the cornerstone of effective HPP therapy, whether receiving ERT or not
- *Asfotase alfa*, to date reported in infants and children, targets the underlying pathophysiology with greater precision than any available therapy
- With *asfotase alfa* now available multi-nationally, further studies are needed to understand the full effects of the drug on the underlying phenotype across the ages and clinical spectrum
- Attempts to alleviate symptoms of the disease through optimization of bone mass or to increase production of osteoblasts and ALP have led to mixed results
- Whether *second and third generation bisphosphonates* can improve bone strength through their effects on bone modeling in the growing child with HPP is unclear
Acknowledgements

• Dr. Cheryl Greenberg
  – University of Manitoba
• Dr. Marc McKee
  – McGill University
• Dr. Frank Rauch
  – McGill University