X-linked hypophosphatemic rickets: New Clinical Practice Recommendations

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ERKNet
The European Rare Kidney Disease Reference Network

MEDIZINISCHE HOCHSCHULE
HANNOVER

ERKNet Webinar
June 25, 2019
Disclosures

**Speaker fees/consultancy:** Amgen, Chiesi, Horizon, Kyowa Kirin, Merck-Serono, Pfizer, Sandoz

**Research grants:** Amgen, Kyowa Kirin, Horizon, Sandoz
Introduction (1/2)

• XLH is the most common cause of inherited phosphate wasting\(^1\)
  - Incidence: 3.9/100,000 live births
  - Prevalence: 1.7–4.8/100,000

• Characterised by renal phosphate wasting (resulting in hypophosphatemia) and reduction in 1,25(OH)\(_2\) vitamin D synthesis\(^1\)

• Key clinical characteristics include rickets, disproportionate short stature and osteo- and odontomalacia\(^1\)

• Children usually present with clinical symptoms within the first two years of life, but diagnosis is often delayed due to the diversity of clinical manifestations and the rarity of the disease\(^1\)

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Pathophysiology of rickets in XLH\(^2\)

NaPi, sodium–phosphate co-transporter; Pi, phosphate

Introduction (2/2)

• Diagnosis and management of patients with XLH is challenging; there are currently no evidence-based, systematically developed recommendations
  – An initiative, launched by ESPN, was carried out between June 2017 and June 2018 to develop recommendations for the diagnosis and management of patients with XLH

• These clinical practice recommendations were endorsed by the:
  – ESPN, ESPE, ESE, Endo-ERN, BOND; IOF: Skeletal Rare Diseases Working Group, ECTS, EPOS study group on Metabolic and Genetic Bone Disorders, European Society of Craniofacial Surgery, European Society of Paediatric Neurosurgery, EFP
Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia

Abstract | X-linked hypophosphataemia (XLH) is the most common cause of inherited phosphate wasting and is associated with severe complications such as rickets, lower limb deformities, pain, poor mineralization of the teeth and disproportionate short stature in children as well as hyperparathyroidism, osteomalacia, enthesopathies, osteoarthritis and pseudofractures in adults. The characteristics and severity of XLH vary between patients. Because of its rarity, the diagnosis and specific treatment of XLH are frequently delayed, which has a detrimental effect on patient outcomes. In this Evidence-Based Guideline, we recommend that the diagnosis of XLH is based on signs of rickets and/or osteomalacia in association with hypophosphataemia and renal phosphate wasting in the absence of vitamin D or calcium deficiency. Whenever possible, the diagnosis should be confirmed by molecular genetic analysis or measurement of levels of fibroblast growth factor 23 (FGF23) before treatment. Owing to the multisystemic nature of the disease, patients should be seen regularly by multidisciplinary teams organized by a metabolic bone disease expert. In this article, we summarize the current evidence and provide recommendations on features of the disease, including new treatment modalities, to improve knowledge and provide guidance for diagnosis and multidisciplinary care.

*Haffner D et al. Nat Rev Nephrol 2019*
Clinical Practice Recommendations: Outline

• Methodology overview

• Clinical practice recommendations
  − Diagnosis in children and adults
    • Clinical and molecular diagnosis
    • Patient work-up and differential diagnosis
  − Follow-up
  − Treatment in children
  − Treatment in adults
  − Other management/treatment recommendations (e.g. orthopaedics, **dental**, hearing, musculoskeletal system, neurosurgical, lifestyle…)

• Conclusions

• Future research

=> Presentation of 40% of the recommendations (28/69 slides)
Methodology: overview

The project followed the RIGHT Statement for Practice Guidelines and the grading from the AAP for grading evidence quality.

Recommendations developed by the core leadership group based on evidence from the literature:
- Specialists from (paediatric) endocrinology; paediatric nephrology; paediatric orthopaedic surgery; rheumatology; dentistry; neurosurgery
- Representatives from XLH patient organisations

Proposed recommendations shared with a voting group via an e-questionnaire (Delphi method; 5-point scale)

Voting group (N=41):
- Members of supporting societies and networks with expertise in paediatric and adult XLH

<70% consensus
Recommendations discussed and modified by the core group

≥70% consensus
Recommendation accepted

AAP, American Academy of Pediatrics; RIGHT, Reporting Items for practice Guidelines in HealThcare.

Haffner D et al. Nat Rev Nephrol 2019
Methodology: evidence generation

- **PICO* elements for literature search**
  - **Population:** children and adults with XLH
  - **Intervention and comparators:** benefit of treatment versus no treatment; patient status at baseline versus post treatment
  - **Outcomes addressed:** recommendations for diagnosis, follow-up and treatment based on the following:
    - Bone disease
    - Growth
    - Treatment- or disease-associated complications
    - Comorbidities

- **PubMed database search (up to 26 June 2018)**
  - **Study types:** Prospective randomised controlled clinical trials; uncontrolled or observational studies; registries; summaries and case reports (restricted to human studies published in English)
  - **Keywords (Mesh terms):** X-linked hypophosphatemia; X-linked hypophosphatemic rickets; hypophosphatemic rickets; familial hypophosphatemic rickets; PHEX; osteomalacia

- **8903 results**
  - (196 articles referenced in recommendations)

- **AAP grading system used to develop recommendations (see next slide for detail)**

Key used throughout the presentation:

- A Strong
- B Moderate
- C Moderate
- D Weak

- B Weak
- C Weak

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*PICO: Patient (or Population), Intervention, Comparison, Outcome.

AAP, American Academy of Pediatrics.

# Methodology: AAP grading system (1/2)

<table>
<thead>
<tr>
<th>Aggregate evidence quality</th>
<th>Benefit or harm predominates</th>
<th>Benefit and harm balanced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
<td>Strong recommendation</td>
<td>Weak recommendation</td>
</tr>
<tr>
<td>AAP grading system (1/2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis:</strong></td>
<td></td>
<td></td>
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<tr>
<td>AAA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level B</strong></td>
<td>Moderate recommendation</td>
<td>Weak recommendation</td>
</tr>
<tr>
<td>Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level C</strong></td>
<td>Weak recommendation</td>
<td>No recommendation may be made</td>
</tr>
<tr>
<td>Single or few observational studies or multiple studies with inconsistent findings or major limitations</td>
<td>(based on low-quality evidence)</td>
<td></td>
</tr>
<tr>
<td><strong>Level D</strong></td>
<td>Strong recommendation</td>
<td>Moderate recommendation</td>
</tr>
<tr>
<td>Expert opinion, case reports, reasoning from first principles</td>
<td></td>
<td></td>
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<tr>
<td><strong>Level X</strong></td>
<td></td>
<td></td>
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<tr>
<td>Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates</td>
<td>Strong recommendation</td>
<td>Moderate recommendation</td>
</tr>
</tbody>
</table>

AAP, American Academy of Pediatrics.

### Methodology: AAP grading system (2/2)

<table>
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</thead>
<tbody>
<tr>
<td><strong>Level A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention:</td>
<td>Strong recommendation</td>
<td></td>
</tr>
<tr>
<td>well-designed and conducted trials, meta-analyses on applicable populations</td>
<td><strong>A Strong</strong></td>
<td></td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>independent gold standard studies of applicable populations</td>
<td></td>
<td><strong>Weak recommendation</strong></td>
</tr>
<tr>
<td><strong>Level B</strong></td>
<td>Moderate recommendation</td>
<td></td>
</tr>
<tr>
<td>Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies</td>
<td><strong>B Moderate</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Level C</strong></td>
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<tr>
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<td>(based on low-quality evidence)</td>
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<tr>
<td>Expert opinion, case reports, reasoning from first principles</td>
<td><strong>D Weak</strong></td>
<td>No recommendation may be made</td>
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<td></td>
<td>Moderate recommendation</td>
<td></td>
</tr>
</tbody>
</table>

AAP, American Academy of Pediatrics.

## Diagnosis: children and adults

### Children

A diagnosis of XLH should be considered in the presence of:
- Clinical and/or radiological signs of rickets
- Impaired growth velocity
- Serum phosphate levels below age-related reference range associated with renal phosphate wasting, in the absence of vitamin D or calcium deficiency

### Adults

A diagnosis of XLH should be considered in the presence of:
- Lower limb deformities (or history of)
- Osteomalacia (clinical and/or radiological signs)
  - Including pseudofractures, early osteoarthritis and/or enthesopathy
In the context of serum phosphate levels below age-related reference range and renal phosphate wasting

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Haffner D et al. Nat Rev Nephrol 2019

Midwifery Hochschule Hannover
Clinical and molecular diagnosis: all patients with XLH (1/5)

Diagnosis of XLH is based on the association of clinical, radiological and biochemical assessments

**Recommended initial diagnostic work-up**

**Clinical evaluation:**
- Evidence of rickets or growth failure
- Evidence of dental abnormalities
- Signs of craniosynostosis/intracranial hypertension

- Orthopaedic assessment of the musculo-skeletal system should be performed in the presence of lower limb deformity (*varum* or *valgus* or antero-posterior)

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Haffner D *et al.* Nat Rev Nephrol 2019
Clinical and molecular diagnosis: all patients with XLH (2/5)

Diagnosis of XLH is based on the association of clinical, radiological and biochemical assessments.

Recommended initial diagnostic work-up

Radiological evaluation:
• Diagnose and grade rickets and osteomalacic lesions

Haffner D et al. Nat Rev Nephrol 2019
Clinical and molecular diagnosis: all patients with XLH (3/5)

Diagnosis of XLH is based on the association of clinical, radiological and biochemical assessments

Recommended initial diagnostic work-up

Biochemical tests:
- Serum levels of Pi, Ca, ALP, PTH, 25(OH) vitamin D, 1,25(OH)\(_2\) vitamin D, creatinine
- Urinary Ca, Pi and creatinine (spot urine)
  => Calculation of:
    - Renal phosphate threshold concentration (TmP/GFR)
    - Urinary calcium/creatinine ratio
- Exclude non-selective renal tubular phosphate wasting (suggesting renal Fanconi syndrome) by looking for abnormal serum bicarbonate, amino acid, glucose and/or uric acid losses in urines, and low molecular weight proteinuria

ALP, alkaline phosphatase; Ca, calcium; Pi, phosphate; TmP/GFR, tubular reabsorption of phosphate per glomerular filtration rate.

Haffner D et al. Nat Rev Nephrol 2019
## Biochemical features of XLH (children and adults) (4/5)

<table>
<thead>
<tr>
<th>Typical biochemical features of XLH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum phosphorus</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>ALP</td>
</tr>
<tr>
<td>↑</td>
</tr>
<tr>
<td>TmP/GFR</td>
</tr>
<tr>
<td>↓</td>
</tr>
<tr>
<td>Serum calcium concentration</td>
</tr>
<tr>
<td>Lower normal range</td>
</tr>
<tr>
<td>Urinary calcium</td>
</tr>
<tr>
<td>Low*</td>
</tr>
<tr>
<td>PTH</td>
</tr>
<tr>
<td>Upper limit of normal range or slightly elevated</td>
</tr>
<tr>
<td>1,25(OH)(_2) vitamin D</td>
</tr>
<tr>
<td>Low or inappropriately normal in the setting of hypophosphatemia</td>
</tr>
<tr>
<td>Intact FGF23 (untreated patients)</td>
</tr>
<tr>
<td>↑†</td>
</tr>
</tbody>
</table>

*Due to impaired 1,25(OH)\(_2\) vitamin D synthesis and decreased intestinal calcium absorption; †Normal levels of FGF23 do not exclude a diagnosis of XLH; ALP, alkaline phosphatase; TmP/GFR, tubular reabsorption of phosphate per glomerular filtration rate; PTH, parathyroid hormone. Haffner D et al. *Nat Rev Nephrol* 2019
Clinical and molecular diagnosis: all patients with XLH (5/5)

We recommend confirming the clinical diagnosis of XLH by genetic analysis of the *PHEX* gene in children and adults if feasible

- Negative test result: consider other causes of hypophosphatemia
- If genetic analysis is not available, the presence of elevated plasma intact FGF23 concentrations and/or a positive family history for XLH support the diagnosis
Differential diagnoses (1/6)

- Low serum levels of phosphate
  - Measure serum levels of PTH
    - Normal or low
      - Measure urine levels of phosphate
        - Low
          - Insufficient phosphate intake
          - Decrease in gastrointestinal absorption of phosphate
          - Internal redistribution
          - Enhanced extra-renal removal of phosphate from the body
        - High
          - Measure serum levels of FGF23
            - Normal or low
              - Hereditary hypophosphataemic rickets with hypercalciuria
              - Fanconi syndrome
            - High
              - Hereditary hypophosphataemic rickets (including XLH)
              - Acquired forms of hypophosphataemic rickets due to high levels of FGF23

- Abnormalities in vitamin D metabolism
- Calcium deficiency
- Primary hyperparathyroidism

Enhanced extra-renal removal of phosphate
Internal redistribution
Decrease in phosphate intake
Removal of phosphate from the body

Low serum levels of phosphate — namely hypophosphataemia. Adapted with permission from NATURE 23 (FGF23). Further details of individual entities can be found in

Low serum levels of phosphate: Low serum levels of phosphate

Normal or low: Normal or low

High: High

FGF23: FGF23

XLH: XLH

Rickets: Rickets

Parathyroidectomy: Parathyroidectomy

Hyperparathyroidism: Hyperparathyroidism

Burosumab: Burosumab

Rickets Severity Score (RSS): Rickets Severity Score

Radiographic Global Impression of Change (RGI): Radiographic Global Impression of Change

Orthopedic Society of North America Outcomes Data: Orthopedic Society of North America Outcomes Data

Rickets: Rickets

X-linked hypophosphataemia (XLH): X-linked hypophosphataemia

Orthopedic Society of North America: Orthopedic Society of North America

Haffner D et al. Nat Rev Nephrol 2019
### Differential diagnoses (4/6)

<table>
<thead>
<tr>
<th>Disorder (OMIM#)</th>
<th>Gene/location</th>
<th>Ca</th>
<th>P</th>
<th>ALP</th>
<th>UCa</th>
<th>U_P</th>
<th>TmP/GFR</th>
<th>FGF23</th>
<th>PTH</th>
<th>25 (OH) vitamin D*</th>
<th>1,25 (OH)2 vitamin D</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>XLH (OMIM#307800)</strong></td>
<td>PHEX/Xp22.1</td>
<td>N</td>
<td>↓</td>
<td>↑,↑↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>N↑</td>
<td>N2</td>
<td>↑ FGF23 expression in bone and impaired FGF23 cleavage</td>
</tr>
<tr>
<td><strong>ADHR (OMIM#193100)</strong></td>
<td>FGF23/12p13.3</td>
<td>N</td>
<td>↓</td>
<td>↑,↑↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>N↑</td>
<td>N2</td>
<td>FGF23 protein resistant to degradation</td>
</tr>
<tr>
<td><strong>ARHR1 (OMIM#241520)</strong></td>
<td>DMP1/4q22.1</td>
<td>N</td>
<td>↓</td>
<td>↑,↑↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>N↑</td>
<td>N2</td>
<td>↑ FGF23 expression in bone</td>
</tr>
<tr>
<td><strong>ARHR2 (OMIM#613312)</strong></td>
<td>ENPP1/6q23.2</td>
<td>N</td>
<td>↓</td>
<td>↑,↑↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>N↑</td>
<td>N2</td>
<td>↑ FGF23 expression in bone</td>
</tr>
<tr>
<td><strong>ARHR3 (OMIM#259775)</strong></td>
<td>FAM20C/7q22.3</td>
<td>N</td>
<td>↓</td>
<td>↑,↑↑</td>
<td>?</td>
<td>↑</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>N↑</td>
<td>N2</td>
<td>↑ FGF23 expression in bone</td>
</tr>
</tbody>
</table>

*Cave: prevalence of vitamin D deficiency was reported to be <50% in healthy children; PTM may be moderately elevated; *decreased relative to the serum phosphate concentration; ▼ = decreased; ▼▼ = very decreased; 1,25(OH)2D, 1,25-dihydroxyvitamin; 25(OH)D, cholecalciferol; ADHR, autosomal dominant hypophosphatemic rickets; ARHR1, autosomal dominant hypophosphatemic rickets 1; ARHR2, autosomal recessive hypophosphatemic rickets 2; ARHR3, Raine syndrome associated; ALP, alkaline phosphatase; Ca, serum calcium; FD, fibrous dysplasia P, serum phosphate; PTH, parathyroid hormone; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate normalised to the glomerular filtration rate; UCa, urinary calcium excretion; U_P, urinary phosphate excretion.
### Differential diagnoses (5/6)

<table>
<thead>
<tr>
<th>Disorder (OMIM#)</th>
<th>Gene/location</th>
<th>Ca</th>
<th>P</th>
<th>ALP</th>
<th>UCa</th>
<th>U</th>
<th>TmP/GFR</th>
<th>FGF23</th>
<th>PTH</th>
<th>25 (OH) vitamin D*</th>
<th>1,25 (OH)₂ vitamin D</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rickets/osteomalacia with renal tubular phosphate wasting due to elevated FGF23 levels/signalling (continued)</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Fibrous dysplasia (OMIM#174800)</td>
<td>GNAS/20q13.3</td>
<td>N, ↓</td>
<td>↓</td>
<td>↑↑↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>N, ↑</td>
<td>N, ↑↑</td>
<td>N</td>
<td>N↑</td>
<td>↑ FGF23 expression in bone</td>
</tr>
<tr>
<td>Tumour induced osteomalacia</td>
<td>NA</td>
<td>N, ↓</td>
<td>↓</td>
<td>↑↑↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>N, ↑</td>
<td>N, ↑↑</td>
<td>N</td>
<td>N↑</td>
<td>↑ FGF23 expression in tumour cells</td>
</tr>
<tr>
<td>Cutaneous hypophosphatemia syndrome (SFM; OMIM#163200)</td>
<td>RAS/1p13.2</td>
<td>N, ↓</td>
<td>↓</td>
<td>↑↑↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>N, ↑</td>
<td>N, ↑↑</td>
<td>N</td>
<td>N↑</td>
<td>?</td>
</tr>
<tr>
<td>Osteoglophonic dysplasia (OMIM#166250)</td>
<td>FGFR1/8p11.23</td>
<td>N</td>
<td>↓</td>
<td>↑, N</td>
<td>N</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>N, ↑↑</td>
<td>N</td>
<td>N↑</td>
<td>↑ FGF23 expression in bone</td>
</tr>
<tr>
<td>Hypophosphatemic rickets and hyperparathyroidism (OMIM#612089)</td>
<td>KLOTHO/13q13.1</td>
<td>N</td>
<td>↓</td>
<td>↑↑↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑↑</td>
<td>N</td>
<td>N↑</td>
<td>Unknown; translocation of the KLOTHO promoter</td>
</tr>
</tbody>
</table>

*Cave: prevalence of vitamin D deficiency was reported to be <50% in healthy children; ↑PTH may be moderately elevated; †Decreased relative to the serum phosphate concentration; ↓ = decreased, ↑ = elevated; ↑↑ = very elevated
1,25(OH)₂D, 1,25-dihydroxyvitamin; 25(OH)D, cholecalciferol; ALP, alkaline phosphatase; Ca, serum calcium; P, serum phosphate; PTH, parathyroid hormone; SFM, cutaneous skeletal hypophosphatemia syndrome; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate normalised to the glomerular filtration rate; UCa, urinary calcium excretion; U, urinary phosphate excretion
## Differential diagnoses (6/6)

<table>
<thead>
<tr>
<th>Disorder (OMIM#)</th>
<th>Gene/location</th>
<th>Ca</th>
<th>P</th>
<th>ALP</th>
<th>U$_{Ca}$</th>
<th>U$_{P}$</th>
<th>TmP/GFR</th>
<th>FGF23</th>
<th>PTH</th>
<th>$25 \ (OH)$ vitamin D</th>
<th>$1,25 \ (OH)_{2}$ vitamin D</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rickets/osteomalacia due to primary renal tubular phosphate wasting</strong></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary hypophosphatemic rickets with hypercalciuria (OMIM#241530)</td>
<td>SLC34A3/9q34.3</td>
<td>N</td>
<td>↓</td>
<td>↑↑</td>
<td>N, ↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>Low N, ↓</td>
<td>N</td>
<td>↑↑</td>
<td>Loss of function of NaPi2c in the proximal tubule</td>
</tr>
<tr>
<td>X-linked recessive hypophosphatemic rickets (OMIM#300554)</td>
<td>CLCN5/Xp11.23</td>
<td>N</td>
<td>↓</td>
<td>↑↑</td>
<td>N, ↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>Varies</td>
<td>Varies</td>
<td>N</td>
<td>↑</td>
</tr>
<tr>
<td>NPHLOP1 (OMIM#612286) FRTS2 (OMIM#613388)</td>
<td>SLC34A1/5q35.3</td>
<td>N</td>
<td>↓</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>Varies</td>
<td>Varies</td>
<td>N</td>
<td>↑</td>
</tr>
<tr>
<td>Cystinosis (OMIM#219800) and other hereditary forms of Fanconi syndrome</td>
<td>CTNS/17p13.2</td>
<td>N, ↓</td>
<td>↓</td>
<td>↑↑</td>
<td>N, ↑</td>
<td>↑</td>
<td>N, ↓</td>
<td>N, ↑↑</td>
<td>N, ↑↑</td>
<td>N</td>
<td>N$^*$</td>
<td>Cysteine accumulation in the proximal tubule</td>
</tr>
<tr>
<td>Latrogenic proximal tubulopathy</td>
<td>NA</td>
<td>N</td>
<td>↓</td>
<td>↑↑</td>
<td>Varies</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>Varies</td>
<td>N</td>
<td>↑</td>
<td>Drug toxicity</td>
</tr>
</tbody>
</table>

*Cave: prevalence of vitamin D deficiency was reported to be <50% in healthy children; $^*$depending on the stage of chronic kidney disease; $^\dagger$decreased relative to the serum phosphate concentration; $^\bar{\dagger}$decreased; $^\dagger$ = elevated; $^\dagger\dagger$ = very elevated; $^\dagger \dagger\dagger$ = may range widely

1,25(OH)$_2$D, 1,25-dihydroxyvitamin; 25(OH)D, cholecalciferol; ALP, alkaline phosphatase; Ca, serum calcium; FRTS2, Fanconi reno-tubular syndrome 2;NPHLOP1, hypophosphatemia and nephrocalcinosis; P, serum phosphate; PTH, parathyroid hormone; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate normalised to the glomerular filtration rate; UCa, urinary calcium excretion; UP, urinary phosphate excretion

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Recommended follow-up: all patients with XLH (1/2)

<table>
<thead>
<tr>
<th>Frequency of visits</th>
<th>0–5 years</th>
<th>5 years to start of puberty (9–12 years)</th>
<th>Puberty</th>
<th>Transition to adult care</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, weight, IMD, ICD</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Head circumference, skull shape</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rickets, pain, stiffness, fatigue</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓*</td>
</tr>
<tr>
<td>Musculoskeletal function, 6MWT†</td>
<td></td>
<td>Once a year</td>
<td>Once a year</td>
<td>✓</td>
<td>Once a year</td>
</tr>
<tr>
<td>Orthopaedic examination</td>
<td>Once a year in the presence of significant leg bowing</td>
<td>✓</td>
<td></td>
<td>Once a year‡</td>
<td></td>
</tr>
<tr>
<td>Dentist</td>
<td>Twice a year after tooth eruption</td>
<td>Twice a year</td>
<td>✓</td>
<td></td>
<td>Twice a year</td>
</tr>
<tr>
<td>Hearing</td>
<td></td>
<td>From 8 years: hearing evaluation, repeated if symptoms of hearing difficulties</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The clinical, biochemical and radiological features and complications of XLH vary widely from patient to patient, and thus, treatment and monitoring ultimately should be tailored to the patient based on the individual’s clinical manifestations, medical history, stage of development and the clinician’s professional judgement.

*Also search for osteomalacia, pseudofractures, osteoarthritis and enthesopathy; †If available; ‡in symptomatic patients

6MWT, 6 minutes walk test; ICD, intercondylar distance; IMD, intermalleolar distance

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# Recommended follow-up: all patients with XLH (2/2)

<table>
<thead>
<tr>
<th>Frequency of visits</th>
<th>0–5 years</th>
<th>5 years to start of puberty (9–12 years)</th>
<th>Puberty</th>
<th>Transition to adult care</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum: ALP (children), BAP (adults), calcium, phosphate, PTH, creatinine, eGFR</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>25(OH) vitamin D</td>
<td>Once a year</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Urine: calcium/creatinine ratio*</td>
<td>Every 3–6 months on conventional treatment and burosumab treatment</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fasting serum P and TmP/GFR</td>
<td>On burosumab treatment: Every 2 weeks during the first month, every 4 weeks during the following 2 months and thereafter as appropriate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Twice a year</td>
<td>Twice a year</td>
<td>Twice a year</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Renal ultrasound</td>
<td>Every 1–2 years while undergoing treatment with either conventional or burosumab treatment</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Left wrist and/or lower limbs radiographs</td>
<td>If leg bowing does not improve upon treatment (children)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dental orthopantogram</td>
<td>Not feasible</td>
<td>Based on clinical needs</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Funduscopy and brain MRI</td>
<td>If aberrant shape of skull, headaches or neurological symptoms</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cardiac Ultrasound†</td>
<td>In presence of persistent elevated BP (&gt;95. percentile)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Quality of life‡</td>
<td>Every 2 years§</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Upper normal range (mol/mol): 2.2 (<1 year), 1.4 (1–3 years), 1.1 (3–5 years), 0.8 (5–7 years), 0.7 (>7 years); †According to international guidelines; ‡Using age-appropriate and disease-appropriate QOL scales; §If available ALP, alkaline phosphatase; BAP, bone alkaline phosphatase; eGFR, estimated glomerular filtration rate (Schwartz formula in children, MDRD or CKD-EPI equation in adults); MRI, magnetic resonance imaging; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate normalised to the glomerular filtration rate; QOL, quality of life.

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Follow-up: children with XLH

At least every 3 months during the phases of rapid growth (infancy and puberty) or after initiation of therapy
At least every 6 months in patients showing positive response to treatment and/or stable condition

- Height, weight, head circumference (<5 years), ICD and IMD, and BP
- Measure BMI and annual height velocity
- Perform radiographs* of the left wrist and/or knees if patients:
  - Do not respond well to therapy
  - Worsen in their bone deformity under medical treatment
  - Require orthopaedic surgery
  - Complain of unexplained bone pain
- Or, adolescents with persistent lower limb deformities when they are transitioning to adult care

Recommended analyses

- Search for hearing loss
- Monitor spine deformity and scoliosis, manifestations related to craniosynostosis, Chiari 1 malformation and/or cranial hypertension, and maxillary dysmorphosis
- Record head shape, history of headaches, dental abscesses or maxillofacial cellulitis, bone pain, fatigue, physical function
- Assess bone age to evaluate the growth potential >5 years of age in children with growth impairment
- In the presence of lower limb deformity, perform orthopaedic assessment

*Radiographs should be standardised anterior-posterior standing long leg radiographs (utilising low-dose EOS® when feasible) to assess limb deformities, joint alignment, and bone quality. BMI, body mass index; BP, blood pressure; ICD, intercondylar distance; IMD, intermalleolar distance

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Follow-up in all patients with XLH: biochemical recommendations

- **Blood:**
  - Monitor ALP (total serum ALP in children and BAP in adults), calcium, phosphate, creatinine, PTH, 25(OH) vitamin D
- **Urine:**
  - Calculate urinary calcium/creatinine ratio in patients receiving conventional or burosumab treatment

**In patients receiving burosumab treatment, it is also recommended to:**

- Monitor fasting serum phosphate together with TmP/GFR
  - every 2 weeks during the first month, every 4 weeks for the following 2 months (and thereafter as appropriate)
- Measure fasting serum phosphate 4 weeks after dose adjustment
- Measure 1,25(OH)₂ vitamin D serum levels every 6 months analysed together with the urinary calcium excretion as safety parameters

ALP, alkaline phosphatase; BAP, bone-specific alkaline phosphatase; PTH, parathyroid hormone; TmP/GFR, maximum rate of renal tubular reabsorption of phosphate normalised to the glomerular filtration rate

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We recommend treating children with overt XLH phenotype with a combination of oral phosphorous (phosphate salts) and active vitamin D (calcitriol or alfacacidol) as soon as diagnosis is established.
Conventional treatment in children with XLH: recommendations (2/5)

Phosphorous

- **Infants/pre-school children**: Initial dose: 20–60 mg/kg/day of elemental phosphorous (0.7-2.0 mmol/kg) (adjusted according to improvement of rickets, growth, ALP and PTH levels)

- **Young patients with high ALP levels**: frequent administration of phosphorous (4–6 times per day; lowered to 3–4 times per day when ALP has normalised)

- **Progressive increase in dose (but not >80 mg/kg/day)** to prevent gastrointestinal discomfort and hyperparathyroidism. If present, adjust treatment by decreasing dose and/or increasing the frequency

- **Use lower dose in milder phenotypes** (e.g. infants diagnosed by family screening)

ALP, alkaline phosphatase; PTH, parathyroid hormone

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Conventional treatment in children with XLH: recommendations (3/5)

Active vitamin D

- **Initial dose of calcitriol**: 20–30 ng/kg/day
  OR
- **Initial dose of alfacalcidol**: 30–50 ng/kg/day
  OR
- Treatment can be started empirically at 0.5 μg/day of calcitriol or 1 μg of alfacalcidol (age >12 months) and adjusted based on the clinical and biochemical responses

Native vitamin D

- **Vitamin D deficiency**: Cholecalciferol or ergocalciferol supplements
Conventional treatment in children with XLH: recommendations (4/5)

- **To prevent nephrocalcinosis:**
  - Maintain calciuria levels within the normal range
  - Avoid large doses of phosphate supplements
  - Adopt measures to decrease urinary calcium concentration, excretion, and/or crystallisation if necessary

- **In the event of secondary hyperparathyroidism:**
  - In patients with elevated PTH levels: increase active vitamin D, and/or decrease dose of oral phosphate supplements
  - Calcimimetics may be considered in persistent secondary hyperparathyroidism despite the above measures
  - Parathyroidectomy considered in tertiary hyperparathyroidism

**Note:**

- PTH, parathyroid hormone

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Burosumab treatment in children with XLH: recommendations (1/2)

If available, we recommend considering burosumab treatment in XLH children aged 1 year or older, and in adolescents with growing skeletons if:

- They have radiographic evidence of overt bone disease
- And they are refractory to conventional therapy
- Or if they experience complications related to conventional therapy
- Or if they are unable to adhere to conventional therapy, presumed that adequate monitoring is feasible

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# Burosumab treatment in children with XLH: recommendations (2/2)

## Treatment administration

<table>
<thead>
<tr>
<th>Treatment administration</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting dose</strong></td>
<td>- 0.4 mg/kg every two weeks subcutaneously</td>
</tr>
</tbody>
</table>
| **Titration**            | - 0.4 mg/kg increments to raise fasting serum phosphate levels to within the lower end of the normal reference range for age, to a maximum dosage of 2.0 mg/kg body weight (maximum dose 90 mg)  
- Burosumab should not be adjusted more frequently than every 4 weeks |
| **Monitoring of serum phosphate** | - Monitor fasting serum phosphate levels between injections:  
  - During titration period: ideally, 7–11 days after the last injection to detect hyperphosphatemia  
  - After achievement of a steady-state (which can be assumed after 3 months of a stable dose): preferentially, directly before injections to detect underdosing |
| **Other dose recommendations** | - Withhold dose if fasting serum phosphate level is above the upper range of normal  
- Burosumab may be restarted at approximately half of the previous dose when serum phosphate concentration is below the normal range |
| **Contraindications**    | - Do not administer:  
  - Alongside conventional treatment  
  - When fasting phosphate levels are within the age-related normal reference range before treatment initiation  
- Or in the presence of severe renal impairment |

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Growth hormone treatment

- Routine treatment with rhGH is not recommended
- Children with short stature may be considered for rhGH therapy, provided that their ALP and PTH levels are well controlled

ALP, alkaline phosphatase; PTH, parathyroid hormone; rhGH, recombinant human growth hormone
Dental treatment in patients with XLH: recommendations

Children and adults with ongoing oral manifestations: treat with active vitamin D + phosphate supplementation to improve dentine mineralisation, reduce the number of dental abscesses and reduce the severity of periodontitis

**Children**
- Standard preventative care plus dental checks once every 6 months
- Seal pits and fissures with flowable resin composite on both temporary and permanent teeth as soon and frequently as required
- Thorough clinical investigation searching for pulp necrosis (colour changes, fistula, swelling, abscess, cellulitis, pain), and performing retrocoronal and/or periapical radiographs or orthopantomogram to search for enlarged pulp chambers and periapical bone loss depending on clinical exam
- Optimise conventional medical treatment of XLH before initiation of orthodontic treatment

**Adults**
- Perform conventional supportive periodontal therapy twice a year
- Implant placement should be performed after 3–6 months of medical treatment
- Medical treatment should be continued for 6 months following implant surgery
- Healing time should be extended up to 6 months

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Take home messages

• The diagnosis of XLH is based on signs of rickets/osteomalacia in association with hypophosphatemia, and renal phosphate wasting in the absence of vitamin D or calcium deficiency. Whenever possible, the diagnosis should be confirmed by molecular genetic analysis or measurement of FGF23 level before treatment.

• Children with overt XLH phenotype should be treated with a combination of phosphate salts and active vitamin D as soon as diagnosis is established.

• If available, burosumab treatment should be considered in XLH children (≥ 1 yr) and adolescents with growing skeletons if:
  – they have radiographic evidence of overt bone disease and they are refractory to conventional therapy;
  – or if they experience complications related to conventional therapy;
  – or if they are unable to adhere to conventional therapy, presumed that adequate monitoring is feasible.
Next webinar

Sept 10,
”Pregnancy in CKD incl. genetic CKD"
by Kathleen Claes, Leuven, Belgium.