X-linked hypophosphatemic rickets: New Clincal Practice Recommendations

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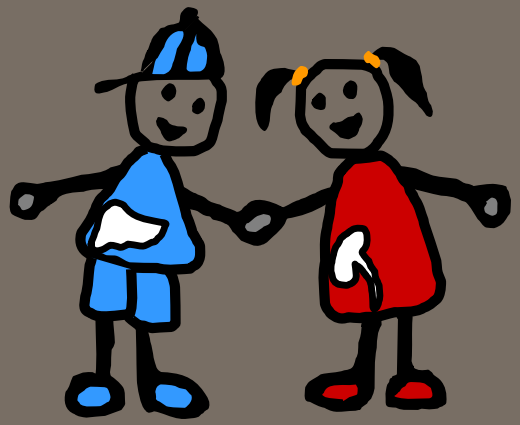

Medizinische Hochschule Hannover

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Disclosures

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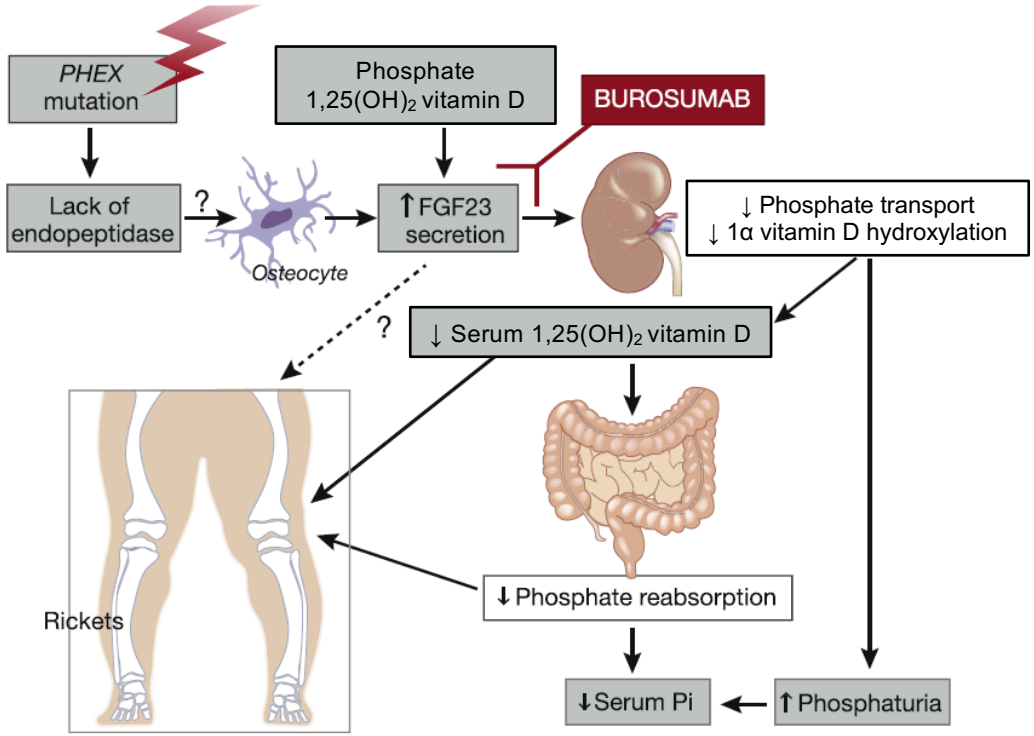
Research grants: Amgen, Kyowa Kirin, Horizon, Sandoz

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]

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

Pathophysiology of rickets in XLH[2]



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

BOND, European Reference Network on Rare Bone Disorders; ECTS, European Calcified Tissue Society; EFP, European Federation of Periodontology; Endo-ERN, European Reference Network on Rare Endocrine Conditions; EPOS, European Paediatric Orthopaedic Society; ESE, European Society of Endocrinology; ESPE, European Society for Paediatric Endocrinology; ESPN, European Society for Paediatric Nephrology; IOF, International Osteoporosis Foundation

CONSENSUS STATEMENT

OPEN

EVIDENCE-BASED GUIDELINE

Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia

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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.

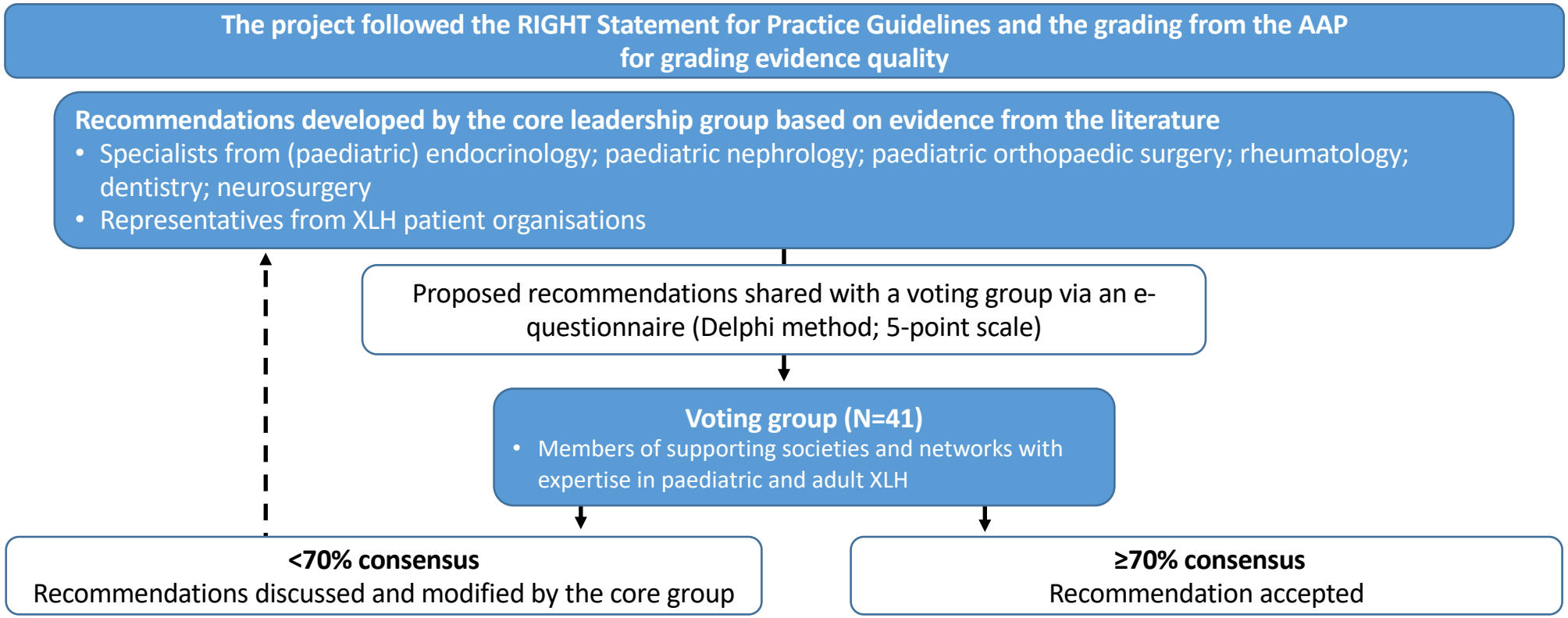
Open Access

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



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

Methodology: evidence generation[1]

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

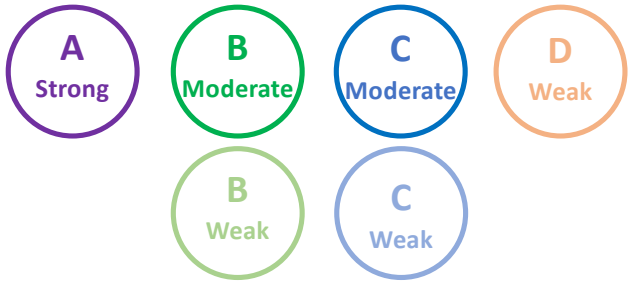
PubMed database search (up to 26 June 2018)

- **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)[1,2]

Key used throughout the presentation:



*PICO: Patient (or Population), Intervention, Comparison, Outcome.
AAP, American Academy of Pediatrics.

1. Haffner D *et al. Nat Rev Nephrol* 2019; 2. American Academy of Pediatrics Steering Committee on Quality Improvement and Management. *Pediatrics* 2004;114:874–877

Methodology: AAP grading system (1/2)

Aggregate evidence quality	Benefit or harm predominates	Benefit and harm balanced
Level A **Intervention:** well-designed and conducted trials, meta-analyses on applicable populations **Diagnosis:** independent gold standard studies of applicable populations	Strong recommendation	Weak recommendation
Level B Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies	Moderate recommendation	
Level C Single or few observational studies or multiple studies with inconsistent findings or major limitations	Weak recommendation	
Level D Expert opinion, case reports, reasoning from first principles	(based on low-quality evidence)	No recommendation may be made
Level X Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates	Strong recommendation Moderate recommendation	

AAP, American Academy of Pediatrics.

Methodology: AAP grading system (2/2)

Aggregate evidence quality	Benefit or harm predominates	Benefit and harm balanced
Level A **Intervention:** well-designed and conducted trials, meta-analyses on applicable populations **Diagnosis:** independent gold standard studies of applicable populations	Strong recommendation (A Strong)	Weak recommendation (B Weak; C Weak)
Level B Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies	Moderate recommendation (B Moderate; C Weak)	
Level C Single or few observational studies or multiple studies with inconsistent findings or major limitations	Weak recommendation (C Moderate)	
Level D Expert opinion, case reports, reasoning from first principles	(based on low-quality evidence) (D Weak)	No recommendation may be made
Level X Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates	Strong recommendation Moderate recommendation	

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 B Moderate
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 B Moderate

Haffner D *et al*. *Nat Rev Nephrol* 2019

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

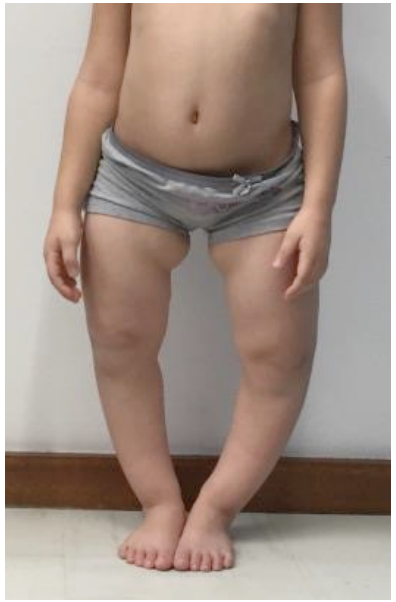
Clinical evaluation:

- Evidence of rickets or growth failure
- Evidence of dental abnormalities
- Signs of craniosynostosis/intracranial hypertension

B Moderate

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

C Moderate



Clinical and molecular diagnosis: all patients with XLH (2/5)

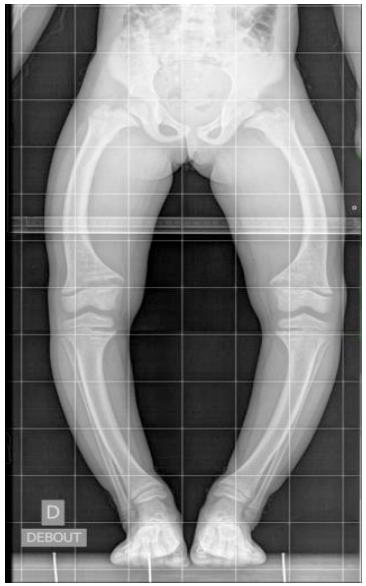
Diagnosis of XLH is based on the association of clinical, radiological and biochemical assessments

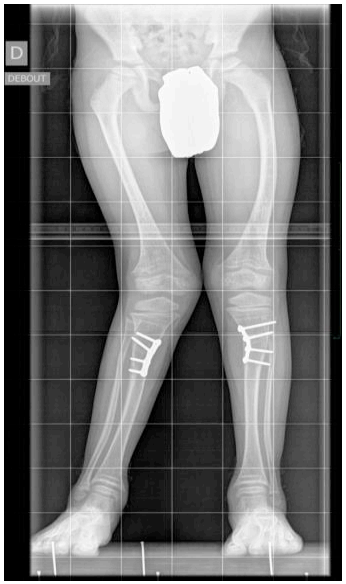
Recommended initial diagnostic work-up

Radiological evaluation:

- Diagnose and grade rickets and osteomalacic lesions

B
Moderate





Haffner D *et al*. *Nat Rev Nephrol* 2019

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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

B Moderate

- 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

B Moderate

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

Biochemical features of XLH (children and adults) (4/5)

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

*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

B Moderate

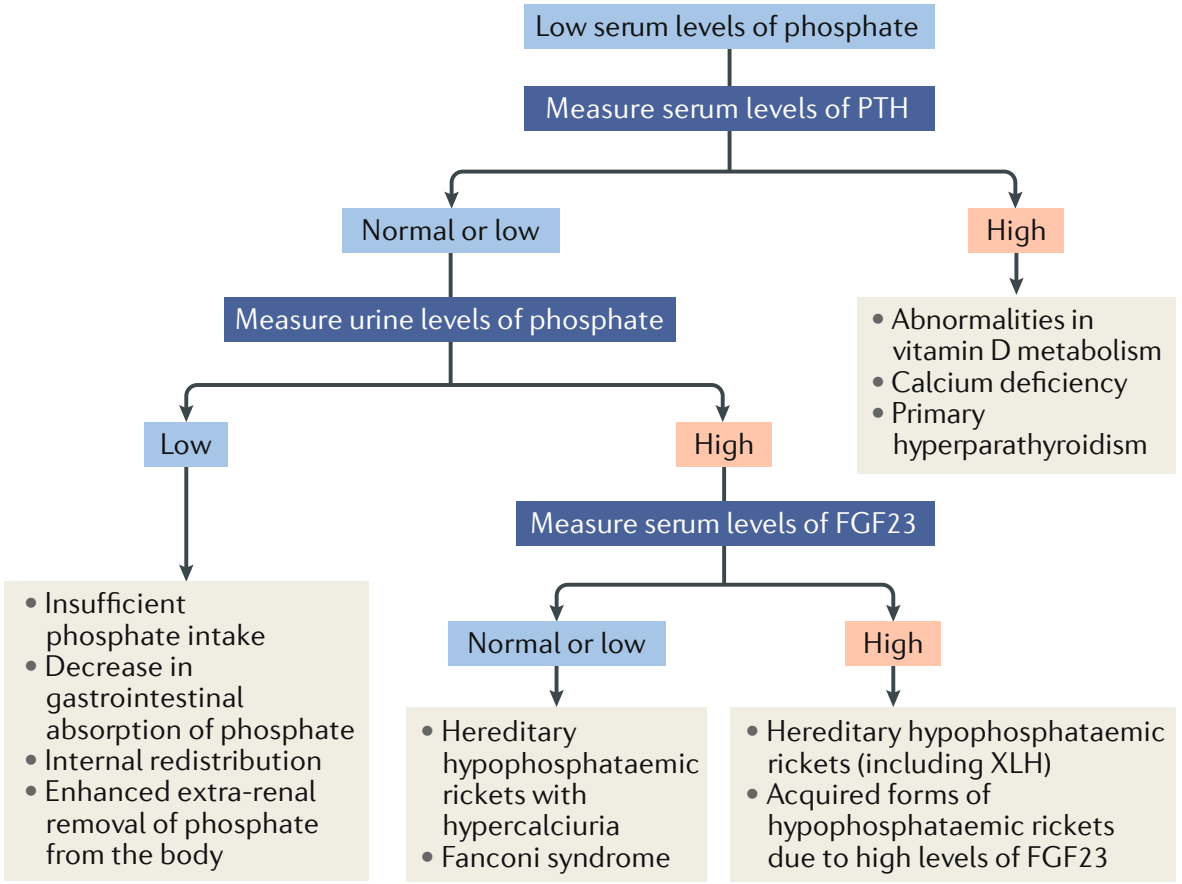
- Negative test result: consider other causes of hypophosphatemia

B Moderate

- 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

C Moderate

Differential diagnoses (1/6)



Haffner D *et al. Nat Rev Nephrol* 2019

Differential diagnoses (4/6)

Disorder (OMIM#)	Gene/location	Ca	P	ALP	U_{Ca}	U_P	TmP/GFR	FGF23	PTH	25 (OH) vitamin D*	1,25 $(OH)_2$ vitamin D	Pathogenesis
Rickets/osteomalacia with renal tubular phosphate wasting due to elevated FGF23 levels/signalling												
XLH (OMIM#307800)	*PHEX*/Xp22.1	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑†	N	N‡	↑ FGF23 expression in bone and impaired FGF23 cleavage
ADHR (OMIM#193100)	*FGF23*/12p13.3	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑†	N	N‡	FGF23 protein resistant to degradation
ARHR1 (OMIM#241520)	*DMP1*/4q22.1	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑†	N	N‡	↑ FGF23 expression in bone
ARHR2 (OMIM#613312)	*ENPP1*/6q23.2	N	↓	↑, ↑↑	↓	↑	↓	↑, N	N, ↑†	N	N‡	↑ FGF23 expression in bone
ARHR3 (OMIM#259775)	*FAM20C*/7q22.3	N	↓	↑, ↑↑	?	↑	↓	↑, N	N, ↑†	N	N‡	↑ FGF23 expression in bone

*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$(OH)_2$D, 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)

Disorder (OMIM#)	Gene/location	Ca	P	ALP	U_{Ca}	U_P	TmP/GFR	FGF23	PTH	25 (OH) vitamin D*	$1,25\ (OH)_2$ vitamin D	Pathogenesis
Rickets/osteomalacia with renal tubular phosphate wasting due to elevated FGF23 levels/signalling (continued)												
Fibrous dysplasia (OMIM#174800)	*GNAS*/20q13.3	N, ↓	↓	↑, ↑↑	↓	↑	↓	N, ↑	N, ↑†	N	N‡	↑ FGF23 expression in bone
Tumour induced osteomalacia	NA	N, ↓	↓	↑, ↑↑	↓	↑	↓	N, ↑	N, ↑†	N	N‡	↑ FGF23 expression in tumour cells
Cutaneous skeletal hypophosphatemia syndrome (SFM; OMIM#163200)	*RAS*/1p13.2	N, ↓	↓	↑, ↑↑	↓	↑	↓	N, ↑	N, ↑†	N	N‡	?
Osteoglophonic dysplasia (OMIM#166250)	*FGFR1*/8p11.23	N	↓	↑, N	N	↑	↓	N	N, ↑†	N	N‡	↑ FGF23 expression in bone
Hypophosphatemic rickets and hyperparathyroidism (OMIM#612089)	*KLOTHO*/13q13.1	N	↓	↑, ↑↑	↓	↑	↓	↑	↑↑	N	N‡	Unknown; translocation of the *KLOTHO* promoter

*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_P, urinary phosphate excretion

Differential diagnoses (6/6)

Disorder (OMIM#)	Gene/location	Ca	P	ALP	U_{Ca}	U_P	TmP/GFR	FGF23	PTH	25 (OH) vitamin D*	1,25 $(OH)_2$ vitamin D	Pathogenesis
Rickets/osteomalacia due to primary renal tubular phosphate wasting												
Hereditary hypophosphatemic rickets with hypercalciuria (OMIM#241530)	*SLC34A3*/9q34.3	N	↓	↑(↑↑)	N, ↑	↑	↓	↓	Low N, ↓	N	↑↑	Loss of function of NaPi2c in the proximal tubule
X-linked recessive hypophosphatemic rickets (OMIM#300554)	*CLCN5*/Xp11.23	N	↓	↑(↑↑)	N, ↑	↑	↓	Varies	Varies	N	↑	Loss of function of CLCN5 in the proximal tubule
NPHLOP1 (OMIM#612286) FRTS2 (OMIM#613388)	*SLC34A1*/5q35.3	N	↓	↑(↑↑)	↑	↑	↓	↓	Varies	N	↑	Loss of function of NaPi2a in the proximal tubule
Cystinosis (OMIM#219800) and other hereditary forms of Fanconi syndrome	*CTNS*/17p13.2	N, ↓	↓	↑(↑↑)	N, ↑	↑	N, ↓	N, ↑†	N, ↑†	N	N‡	Cysteine accumulation in the proximal tubule
Latrogenic proximal tubulopathy	NA	N	↓	↑(↑↑)	Varies	↑	↓	↓	Varies	N	↑	Drug toxicity

*Cave: prevalence of vitamin D deficiency was reported to be <50% in healthy children; †depending on the stage of chronic kidney disease; ‡decreased relative to the serum phosphate concentration;
↓ = decreased, ↑ = elevated; ↑↑ = very elevated; ↑ (↑↑) = 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; U_P, urinary phosphate excretion

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

	0–5 years	5 years to start of puberty (9–12 years)	Puberty	Transition to adult care	Adults
Frequency of visits	Monthly to 3 monthly	3–6 months	3 months		6–12 months
Height, weight, IMD, ICD	✓	✓	✓	✓	✓
Head circumference, skull shape	✓				
Rickets, pain, stiffness, fatigue	✓	✓	✓	✓	✓*
Musculoskeletal function, 6MWT†		Once a year	Once a year	✓	Once a year
Orthopaedic examination	Once a year in the presence of significant leg bowing			✓	Once a year‡
Dentist	Twice a year after tooth eruption	Twice a year		✓	Twice a year
Hearing		From 8 years: hearing evaluation, repeated if symptoms of hearing difficulties			

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

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

	0–5 years	5 years to start of puberty (9–12 years)	Puberty	Transition to adult care	Adults
Frequency of visits	Monthly to 3 monthly	3–6 months	3 months		6–12 months
Serum: ALP (children), BAP (adults), calcium, phosphate, PTH, creatinine, eGFR	✓	✓	✓	✓	✓
25(OH) vitamin D	Once a year			✓	Once a year
Urine: calcium/creatinine ratio*	Every 3–6 months on conventional treatment and burosumab treatment				
Fasting serum P and TmP/GFR	On burosumab treatment: Every 2 weeks during the first month, every 4 weeks during the following 2 months and thereafter as appropriate • Titration period: between injections, ideally 7–11 days after last injection to detect hyperphosphatemia • After achievement of a steady-state: preferentially directly before injections (children) or during the last week before the next injection (adults) to detect underdosing • Also measured 4 weeks after dose adjustment				
$1,25(OH)_2$ vitamin D	On burosumab treatment: Every 3–6 months (analysed together with U_{Ca})				
Blood pressure	Twice a year	Twice a year	Twice a year	✓	Twice a year
Renal ultrasound	Every 1–2 years while undergoing treatment with either conventional or burosumab treatment			✓	Every 1–2 years on treatment
Left wrist and/or lower limbs radiographs	• If leg bowing does not improve upon treatment (children) • If surgery is indicated • Focused on any area of localised persistent bone pain • In case of short stature (bone age assessment)			In adolescents with persistent lower limb deformities when they are transitioning to adult care	
Dental orthopantogram	Not feasible	Based on clinical needs			
Funduscopy and brain MRI	If aberrant shape of skull, headaches or neurological symptoms	If recurrent headaches, declining school/cognitive performances or neurological symptoms			
Cardiac Ultrasound†	In presence of persistent elevated BP (>95. percentile)				
Quality of life‡		Every 2 years§		✓§	Every 2 years§

*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.

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

C Weak

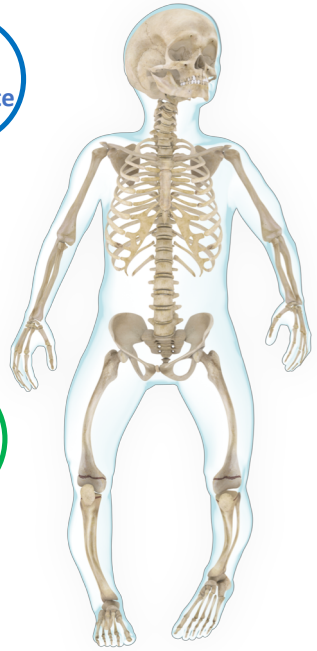
Recommended analyses

- Height, weight, head circumference (<5 years), ICD and IMD, and BP
- Measure BMI and annual height velocity

C Moderate

- 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

B Moderate



- 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

C Moderate

- 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

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

B Moderate

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)

B Moderate

B Weak

- Measure fasting serum phosphate 4 weeks after dose adjustment

B Moderate

- Measure 1,25$(OH)_2$ vitamin D serum levels every 6 months analysed together with the urinary calcium excretion as safety parameters

B Weak

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

Conventional treatment in children with XLH: recommendations (1/5)

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

B
Moderate

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

ALP, alkaline phosphatase; PTH, parathyroid hormone

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 alfacalcidiol**: 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

C Moderate

Native vitamin D

- **Vitamin D deficiency:** Cholecalciferol or ergocalciferol supplements

C Weak

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

C Moderate

- **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

C Moderate

D Weak

C Moderate

PTH, parathyroid hormone

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:

B
Moderate

- **They have radiographic evidence of overt bone disease**
- **<u>And</u> they are refractory to conventional therapy**
- **<u>Or</u> if they experience complications related to conventional therapy**
- **<u>Or</u> 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	
Starting dose	• 0.4 mg/kg every two weeks subcutaneously	
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	B Moderate
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	B Weak
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	B Moderate
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	

Haffner D *et al. Nat Rev Nephrol* 2019

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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

C
Weak

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

B Moderate

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

C Weak

Adults

- Perform conventional supportive periodontal therapy twice a year

B Moderate

- 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

D Weak

- 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

B Weak

- Optimise conventional medical treatment of XLH before initiation of orthodontic treatment

C Moderate

Haffner D *et al*. *Nat Rev Nephrol* 2019

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.

Thank you for your attention !

Medizinische Hochschule Hannover