

X-Linked Hypophosphatemia Management in Children: An International Working Group Clinical Practice Guideline

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Abstract

Context: An International Working Group (IWG) developed new guidelines on the diagnosis, evaluation, management, and monitoring of X-linked hypophosphatemia (XLH) in children. Over the past 5 years, important advances have occurred in our understanding of the presentation, complications, and treatment of XLH.

Methods: A group of 50 international experts in XLH from Canada, the United States, Europe, Asia, and South America, along with methodology experts and a patient partner, held 18 teleconference meetings in 2023-2024. These meetings addressed key issues regarding diagnosing, evaluating, managing, and monitoring XLH in children. Two systematic reviews were conducted to examine the impact of burosumab compared to conventional therapy (phosphate salts and active vitamin D) or no therapy, and to assess the impact of conventional therapy vs no therapy on patient-important outcomes. The certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. Additionally, narrative reviews were completed on XLH diagnosis and the role of genetic testing, and an expert clinical practice survey informed the monitoring recommendations.

Outcomes: An approach to establishing the diagnosis of XLH is presented. GRADEd recommendations were developed on treatment strategies for XLH in children. Monitoring recommendations, GRADEd as weak with very low certainty, were based on clinical practice survey of the IWG experts. The guidelines also addressed dental complications and proposed potential strategies to mitigate them.

Conclusion: These clinical practice guidelines provide an update of the current evidence on the diagnosis and management of XLH and provide a comprehensive guidance for multidisciplinary healthcare professionals involved in the care of children with XLH.

Key Words: X-linked hypophosphatemia (XLH), clinical practice guidelines, consensus, pediatrics, children, rickets

Abbreviations: ALP, alkaline phosphatase; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IWG, international working group; Npt2, renal sodium-phosphate cotransporter 2; PHEX, phosphate-regulating endopeptidase homolog, X-linked; PTH, parathyroid hormone; QoL, quality of life; RCT, randomized controlled trial; rhGH, recombinant human growth hormone; TmP/GFR, tubular maximum phosphate reabsorption adjusted for glomerular filtration rate; VUS, variant of unknown significance; XLH, X-linked hypophosphatemia.

Key Guidance

GRADEd Recommendations

- **Development:** Developed following a structured approach
 - Treatment Recommendations: Based on systematic reviews
 - Monitoring Recommendations: Based on an expert clinical practice survey (very low-quality evidence)
- **Expression of Recommendations:**
 - Strong Recommendations: Expressed as “**We recommend**”
 - Strong:** When the panel was confident that the desirable effects of the intervention outweighed the undesirable ones
 - Weak/Conditional Recommendations: Expressed as “**We suggest**”
 - Weak:** Attributed either to low certainty evidence or to a close balance between the desirable and undesirable effects
 - Conditional:** When the panel concluded that the desirable effects of the intervention probably outweigh the undesirable effects, though there is some uncertainty

Non-GRADEd Recommendations

- **Development:** Based on a narrative review for questions where there was not sufficient evidence to conduct systematic reviews
- **Expression of Recommendations:**
 - Expressed as “**The panel proposes**”

Consensus Development

All recommendations (GRADEd or non-GRADEd) were developed through a consensus reached among the International Working Group (IWG) members across several meetings.

Background

X-linked hypophosphatemia (XLH) is a rare, inherited disorder primarily affecting the skeleton and teeth in children (1). XLH is caused by pathogenic loss-of-function variants in the phosphate-regulating endopeptidase homolog, X-linked (*PHEX*) gene, leading to increased fibroblast growth factor 23 (FGF23) and chronic hypophosphatemia secondary to renal phosphate wasting (2). This manifests as impaired bone mineralization and skeletal deformities in affected children. Loss of *PHEX* protein may also have direct effects on skeletal integrity outside of its effect on FGF23, phosphate, and activated vitamin D, which are currently under study. Other biochemical findings in children may include elevated levels of serum alkaline phosphatase (ALP), although adults with XLH may have normal serum ALP despite frank hypophosphatemia and active osteomalacia.

While dental infections are common in both children and adults with XLH (3), other disease comorbidities such as enthesopathy, arthritis, and spinal stenosis primarily manifest in adulthood (4). This manuscript summarizes current evidence as well as recommendations based on an expert clinical practice survey regarding diagnosis and management of XLH in children. We also provide additional details regarding the features of XLH in children that are important in confirming the diagnosis and in the, monitoring and management of XLH.

Methodology

The recommendations in these guidelines are based on two systematic literature reviews (5); in addition, the monitoring recommendations are based on an expert clinical practice survey, along with a narrative review of the literature, given the limited published evidence on pediatric XLH diagnosis and management (6). The initial assessment and monitoring recommendations were based on experts' clinical practice survey and included only practices performed by at least 80% of experts in 80% or more of their initial evaluations of patients referred for XLH assessment and management. For follow-up assessments, the threshold was set to practices used by at least 80% of experts at least 80% of the time during specific intervals for their existing patients.

These guidelines employed rigorous approaches, including a comprehensive literature review conducted by a specialized healthcare librarian, and duplicate assessment of eligibility, risk of bias, and data abstraction. The evaluation of the quality of evidence from included studies utilized the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology (7), and the systematic reviews were preregistered with PROSPERO (5).

The GRADEd treatment recommendations followed a structured approach, encompassing the formulation of questions in patient/intervention/comparator/outcome (PICO) format (8), conducting systematic literature reviews, and rating the quality of evidence in tables addressing patient-important outcomes (9). The recommendations were classified as strong or weak with a description of the quality of evidence (10, 11). The phrase “*we recommend*” was used for strong recommendations and the phrase “*we suggest*” was used for weak or conditional recommendations. In contrast, the non-GRADEd recommendations did not adhere to a structured approach but were based on narrative reviews of the literature and consensus among the International Working

Group (IWG) panelists. Patients' values and preferences were taken into consideration regarding recommendations (7). The phrase “*the panel proposes*” was used when presenting the non-GRADEd recommendations.

Monitoring recommendations, GRADEd as a very low-quality evidence, were derived from a survey of experts' practices, as there were no published studies that compared the impact of different monitoring approaches. The panel members designed a detailed survey to capture clinical practice among experts in the field. An agreement of at least 80% of panel members was required for a clinical practice to become a recommendation. More details are presented in an accompanying manuscript on XLH monitoring (12).

How to Diagnose?

DIAGNOSIS RECOMMENDATIONS IN CHILDREN (NON-GRADEd)

The panel proposes that

The diagnosis of XLH can be made in the presence of chronic hypophosphatemia and the absence of other conditions resulting in renal phosphate wasting. The diagnosis is supported by an X-linked inheritance pattern. An approach to diagnosis is presented in Fig. 1.

INITIAL ASSESSMENT RECOMMENDATIONS (GRADEd) (Fig. 2)

In all children from infancy to adolescence unless otherwise specified:

We Suggest (*weak recommendations, very low certainty evidence*)*

1. Obtaining and documenting family history of XLH, history of fractures, dental abscess (or maxillofacial cellulitis) in the medical records
2. Assessing pain through age-appropriate clinical interviews and caregiver reports
3. Measuring standing height (recumbent length in children ≤ 2 years), weight, head circumference, and blood pressure measurements expressed as percentiles or Z scores (in addition to an overall pediatric physical examination)
4. Measuring serum phosphorus, calcium corrected for albumin or ionized calcium, ALP, 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, kidney function (creatinine, eGFR), PTH, spot** urine calcium/creatinine ratio (or a 24-hour urine calcium excretion adjusted for weight -normal <4 mg/kg/day- may supplement spot testing in complex cases), and spot urine phosphorus/creatinine for calculation of TRP or TmP/GFR (*All specimens preferred to be morning, fasting for at least 2-3 hours, with serum and urine samples collected simultaneously or within 2 hours of each other*)
5. Genetic testing for variants in the genes resulting in hypophosphatemia, including *PHEX****
6. Obtaining baseline imaging including x-rays of long bones (eg, supine AP of lower extremities for children unable to stand; standing lower extremity views for those able to stand without

assistance) and renal ultrasound to screen for nephrocalcinosis

7. Performing dental assessment including bitewings and/or periapical x-rays, or orthopantomogram, for children ≥ 6 years old, to screen for enlarged pulp chambers, prominent pulp horns, and pulp necrosis (characteristics of the condition)

Practices that we suggest to not routinely order at baseline (thus considered discretionary) due to weak recommendations with very low certainty.

1. Baseline funduscopy examination to exclude papilledema in children ≤ 2 years old in the absence of concerning symptoms such as headache, vomiting, loss of developmental milestones
2. Baseline trans-iliac bone biopsy for histomorphometry
3. X-rays for longitudinal determinations of radiographic global impression of change (RGI-C), for serial follow-up

*Based on clinical practice survey with at least 80% of experts performing the clinical practice at least 80% of the times in 80% or more of their patients attending for an initial assessment.

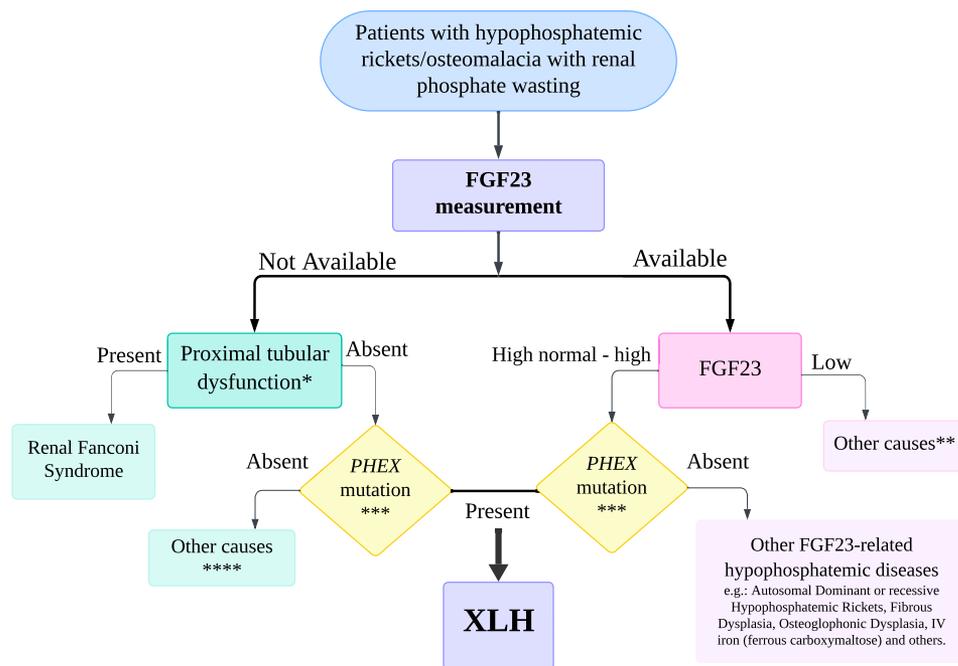
**Normal <0.2 mg/mg (or <1.4 mmol/mmol in some laboratories) in children; age-adjusted norms apply for infants/toddlers.

***Gene panel includes: *FGF23*, *SKG3* (uncertain *FGF23* status), *ENPP*, *DMP1*, *ENPP1*, *FAM20C*, *KLOTHO*, *FGFR1*, *INPPL1*, *RAS*, *GNAS*, *SLC34A1*, *SLC34A3*, *CLCN5*, *CTNS*, *NHERF1*.

Abbreviations: ALP, alkaline phosphatase; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; TRP, tubular reabsorption of phosphate; TmP/GFR, tubular maximum phosphate reabsorption adjusted for glomerular filtration rate; XLH, X-linked hypophosphatemia.

Clinical Manifestations, Biochemical and Radiographic Evaluation in Children and Adolescents

Characteristic clinical features in children include lower limb deformities, dolichocephaly due to craniosynostosis, recurrent dental abscesses, growth delay, impaired muscle strength and endurance, delayed motor milestones, bone pain, and sometimes osteomalacia-related fractures or pseudofractures (13, 14). The Chiari 1 malformation has been described in up to 2.5% of children with XLH (15). Cranial abnormalities may be asymptomatic or associated with headaches, vomiting, papilledema, and neurologic symptoms (13). Syringomyelia may also occur (15, 16). Osteophytes, enthesopathies, and spinal stenosis do not typically develop until adulthood (17). Tinnitus is frequent, even in childhood, and may be associated with overt hearing loss (18).



*Low molecular weight proteinuria, aminoaciduria, renal glycosuria, renal tubular acidosis.

**Proximal tubular dysfunction, vitamin D deficiency, HHRH.

***It is recognized that DNA testing may not be available and it is possible that not all variants in *PHEX* can be detected.

****Other FGF23-related hypophosphatemic diseases besides XLH, HHRH and vitamin D deficiency

Abbreviations: FGF23; fibroblast growth factor 23; HHRH: hereditary hypophosphatemic rickets with hypercalciuria; PHEX: phosphate-regulating endopeptidase homolog, X-linked (*PHEX*) gene; XLH: X-Linked Hypophosphatemia

Figure 1. XLH diagnostic pathway.

Initial Assessment Recommendations in Children (GRADEd)

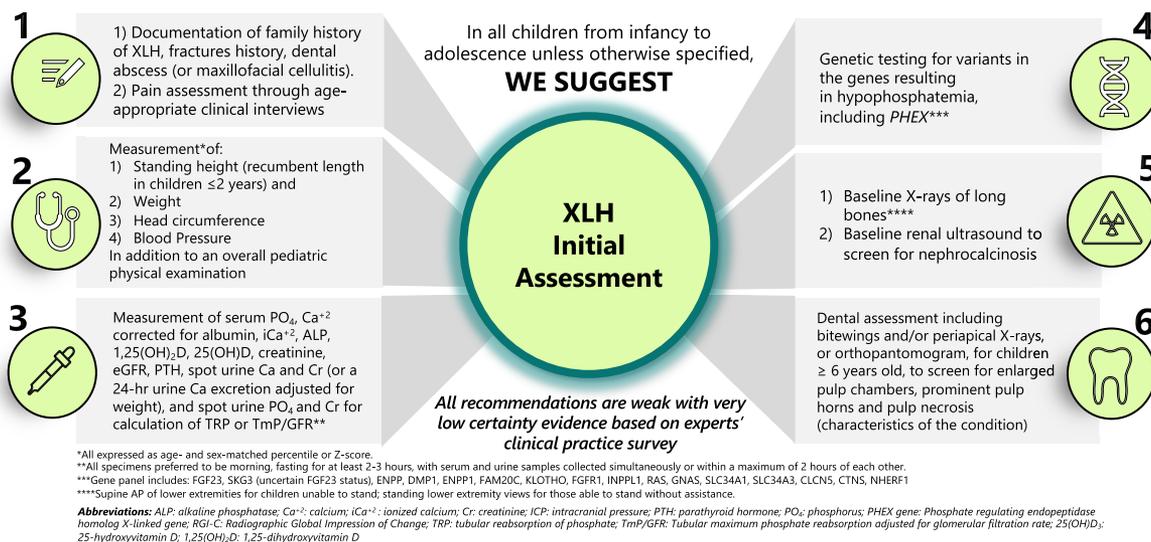


Figure 2. GRADEd initial assessment recommendations in children with XL.

In the newborn period, the serum phosphorus and ALP values are often normal for age, but by 3 months of age, the classic biochemical profile, with hypophosphatemia and increasing ALP, is present in most infants with XLH (Table 1). Circulating parathyroid hormone (PTH) is usually normal or modestly elevated, which distinguishes XLH from the more substantial elevations in ALP and PTH typical of nutritional rickets (19). Consistent with FGF23 overproduction, FGF23 is expected to be inappropriately normal or high, while serum 1,25-dihydroxyvitamin D is usually low or inappropriately normal despite hypophosphatemia (Table 2). Serum phosphorus, ALP, and tubular maximum phosphate reabsorption adjusted for glomerular filtration rate (TmP/GFR) vary with age in childhood; therefore, it is important to use appropriate normative data for age when interpreting results (20).

Table 1. Clinical features of XLH in children

Manifestations
Lower limb deformity
Below average stature
Bone pain
Muscle weakness and fatigue
Dolichocephaly and craniosynostosis
Dental abscesses
Tinnitus, hearing loss

The biochemical profile of children with XLH contrasts with those with nutritional rickets. In nutritional rickets, 25-hydroxyvitamin D levels are usually low, accompanied by decreased serum calcium and phosphorus, with considerable secondary elevations in PTH (19). ALP levels are elevated, although usually to a greater extent than in XLH (21–23). Elevated PTH reduces the abundance of the renal sodium-phosphate cotransporter 2a (Npt2a) and the renal sodium-phosphate cotransporter 2c (Npt2c) in the renal proximal tubules, resulting in renal phosphate wasting (ie, low

Table 2. Biochemical findings in pediatric XLH at diagnosis

Parameter	Value
Serum phosphorus	Low for age, due to renal phosphate wasting
Serum calcium (albumin-adjusted or ionized)	Normal
Serum parathyroid hormone	Normal or mildly elevated
Serum alkaline phosphatase	High
Serum 25-hydroxyvitamin D	Normal (or low if concurrent vitamin D inadequacy)
Serum 1,25-dihydroxyvitamin D	Normal or inappropriately low
Serum fibroblast growth factor 23 (FGF23)	High or inappropriately normal
Urine calcium/creatinine	Normal or low
Tubular maximum reabsorption of Phosphate/Glomerular Filtration Rate (TmP/GFR) (calculator)	Low

Note: Always ensure appropriate age-dependent reference ranges are utilized to prevent missed diagnosis.

TmP/GFR) and subsequent hypophosphatemia, although typically less severe than seen in XLH (24). The biochemical abnormalities of nutritional rickets correct with appropriate supplementation of vitamin D₃ (cholecalciferol) or D₂ (ergocalciferol) along with adequate calcium intake (25), while those of XLH are not corrected with such treatment.

In XLH, imaging studies may reveal rachitic growth plates, lateral femoral bowing, genu varum or valgum, or tibial torsion. Rickets is typically identified at the wrists, knees, and ankles (26, 27).

Role of DNA Analysis

For patients with suspected XLH but without a relevant family history, genetic testing is suggested to confirm that hypophosphatemia is due to disease-causing variants in the

PHEX gene: 1) If there is a known DNA familial variant associated with XLH, then targeted variant testing can be performed and the presence of this variant can support the clinical and biochemical diagnosis. 2) If the genetic variant is unknown in the family, then genetic testing involving any form of testing that sequences the *PHEX* gene (single gene sequence, gene panel, exome or genome) and the finding of a pathogenic or likely pathogenic variant in the *PHEX* gene can support the diagnosis of XLH. 3) In some patients, DNA testing may be negative or may identify a variant of uncertain significance (VUS)—in these cases, the diagnosis of XLH would rely on a clinical or biochemical diagnosis. When a *de novo* variant is identified, the family history may be negative. While there are technologies that can evaluate whether a VUS is damaging (for example if it is novel), these technologies are usually research-based and difficult to access. Since assessment of variants can change over time as new information becomes available, there can be consideration of re-interpretation of the variant classification in the future or assessment through a laboratory or specialist in variant interpretation. 4) If DNA testing was the first test to identify a possible diagnosis of XLH, a clinical and biochemical profile consistent with XLH is required for a diagnosis. Disease manifestations may vary by age and repeat clinical or biochemical evaluation may be necessary if initial testing is negative.

Table 3 presents FGF23-dependent and FGF23-independent hypophosphatemic disorders.

Role of Bone Histomorphometry

Trans-iliac histomorphometry is primarily a research tool and not routinely used in the clinical care of XLH. Trans-iliac bone biopsy could be considered in patients who appear to be having insufficient clinical response to therapies.

Who to Treat?

Natural History and Complications, Both Short-Term and Long-Term, and Impact of Therapy

Early reports of XLH from 1937 to the 1950s described the prominent radiological features, progressive childhood bowing of the legs, anteromedial rotational torsion of tibiae, and short stature, along with the X-linked inheritance (34–36). Dental anomalies, particularly abscess formation, are a prominent feature of the disease (see “Dental and Oral Complications”). Long-term follow-up of adult patients has identified a host of problems that generally worsen through the adult years. Most notably, osteomalacia is evident upon biopsy of untreated patients even in the face of minimal clinical complaints (37). Pseudofractures, particularly of the lower limbs and metatarsals are frequently reported in the adult XLH population, and occur rarely in adolescents, but have not been reported in smaller children with XLH (18, 38). Other nearly universal complications in adulthood include early-onset arthritis and the heterotopic mineralization of tendon and ligaments or enthesopathy, both of which resulting in severe limitations in range of motion which do not appear to reverse with standard therapy (4, 39, 40).

Hearing loss is frequent in adults but may first manifest in childhood. Craniosynostosis, another frequent complication of XLH, is first evident in childhood usually involves the sagittal suture with consequent scaphocephaly (41); related neurological features are discussed below.

Conventional therapy with phosphate supplementation and active vitamin D has been shown to ameliorate some of the XLH features (rickets, lower limb deformity and growth), particularly when initiated in the first year of life (42), but rarely treats or prevents them completely (43). There is no randomized controlled clinical trial (RCT) comparing conventional

Table 3. Disorders with hypophosphatemia

Disease	OMIM Number	Gene(s) Involved
FGF23-dependent		
XLH (X-linked hypophosphatemia)	OMIM#307800	<i>PHEX</i>
ADHR (autosomal-dominant hypophosphatemic rickets)	OMIM#193100	<i>FGF23</i> <i>SKG3</i> (uncertain FGF23 status)
Autosomal-recessive hypophosphatemic rickets	OMIM#241520, #613312, 259775	<i>DMP1</i> , <i>ENPP1</i> , <i>FAM20C</i>
Hypophosphatemic rickets and hyperparathyroidism	OMIM#612089	<i>KLOTHO</i>
Osteoglophonic dysplasia	OMIM#166250	<i>FGFR1</i>
Opsismodysplasia (28)	OMIM#258480	<i>INPPL1</i>
Cutaneous skeletal hypophosphatemia syndrome (RAS)	OMIM#163200	<i>RAS</i>
Fibrous dysplasia	OMIM#174800	<i>GNAS</i>
Tumor-induced osteomalacia (TIO)	N/A	Various/N/A
IV iron (especially ferrous carboxymaltose)	N/A	N/A
FGF23 independent		
Hereditary hypophosphatemic rickets with hypercalciuria (29)	OMIM#241530	<i>SLC34A3</i>
Hypophosphatemia and nephrocalcinosis (30)	OMIM#182309	<i>SLC34A1</i>
X-linked recessive hypophosphatemic rickets: Dent disease (31)	OMIM#300009	<i>CLCN5</i>
Nephropathic cystinosis (32)	OMIM#219800	<i>CTNS</i>
Hypophosphatemia, nephrolithiasis, osteoporosis (33)	OMIM#604990	<i>NHERF1</i>

Table 4. XLH complications involving the kidney

Country [reference]	Number of patients	Percent with complication
Medullary nephrocalcinosis		
Canada (53)	11/23	47.8%
Brazil (51)	15/39	38.5%
Japan (55)	15/18	83.3%
USA (56)	7/41	17.1%
Urinary stone disease		
Brazil (51)	0/39	0.0%
Hypertension		
Japan by median age of 29 (17–2717–27, 34–5034–50, 55)	6/22	27.2%
USA, before age 20 (56)	8/41	19.5%
Tertiary hyperparathyroidism		
USA, before age 20 (56)	11/41	26.8%
Single center from Indiana (mixed adult and pediatric) (57)	14/84	17.0%

therapy with no therapy; however, there is limited evidence in terms of one trial indicating that burosumab is a superior therapy when compared with conventional therapy (44).

Musculoskeletal Manifestations

The skeletal manifestations of XLH in childhood include rickets, impaired growth velocity, waddling gait, and lower limb deformities (45, 46). Children with XLH can present with either varus or valgus deformities as well as increased external torsion of the femur and internal torsion of the tibia (47). Scoliosis may also develop (48–50).

Renal-Related Complications

The most frequent renal complication observed in children with XLH is medullary nephrocalcinosis, reported in 20% to 100% of patients on conventional therapy (51–54). Occasionally nephrolithiasis (usually after childhood) (51) and hypertension may occur, particularly in adults. These and other renal complications are listed in (Table 4). The etiology, timing, and frequency of hypertension onset in childhood is presently under study.

Medullary nephrocalcinosis appears to be relatively benign but progressive decline of GFR may rarely occur (53, 56). Medullary nephrocalcinosis has been associated with higher doses of vitamin D and oral phosphate, and more frequent episodes of hypercalciuria, and thus may be avoidable (53, 58). The extent of medullary hyperechogenicity is often monitored by renal ultrasound at 1- to 2-year intervals, although an optimal frequency has not been established. Lower eGFR has been associated with hypertension but not with nephrocalcinosis; hyperparathyroidism may also be a contributing factor (55). In a North American pediatric cohort, 7/41 had nephrocalcinosis; serum creatinine was normal in all except in one patient affected with persistent hyperparathyroidism and hypertension (56). Of this cohort, 8/41 (19.5%) children developed hypertension in the second decade of life, all preceded by persistent hyperparathyroidism for more than 12 months (56).

Diffuse renal cortical hyperechogenicity may be seen in tertiary hyperparathyroidism while the more typical

nephrocalcinosis pattern is restricted to the renal pyramids (56). The pathogenesis of tertiary hyperparathyroidism is not fully understood. It is likely driven by repeated stimulation of the parathyroid gland from oral phosphate boluses, which can lower serum calcium and eventually lead to autonomous PTH hypersecretion. However, hyperparathyroidism has also been observed in untreated individuals (59, 60). In summary, progressive decline in renal function is unusual in XLH and is usually preceded by hyperparathyroidism and hypertension (56).

Neurologic Manifestations

Neurological complications of XLH in children include headaches, craniosynostosis, Chiari 1 malformation, and syringomyelia (15, 61). In children with XLH, craniosynostosis is due to altered growth and fusion of the osteomalacic cranial bones. Clinical signs associated with craniosynostosis include increased intracranial pressure, vomiting, papilledema, strabismus, and pulsating anterior fontanelle (13). Characteristic calvarial thickening, decreased size of the posterior fossa, and sagittal synostosis predispose those with XLH to the Chiari 1 malformation (a potentially serious complication of the disorder). In an ongoing, multinational, prospective, longitudinal study (XLH-DMP) designed to characterize disease burden, progression and long-term outcomes in XLH, medical history including neurologic complications was reported in 287 children with XLH (62). Craniosynostosis was reported in 54/287 (19%), Chiari 1 malformation in 7/287 (2.4%), syringomyelia in 3/287 (1%), and severe headache in 18/287 (6.3%) (62). In some series of selectively imaged patients, craniosynostosis has been reported in as many as 33% to 59% of children with XLH and Chiari 1 malformation identified in 25% to 44% of children with XLH (15, 61). Neurologic symptoms, including severe headaches, should prompt comprehensive neurologic and fundoscopic examinations. In addition, children with XLH should be examined for cranial morphology, head circumference, conformation of the anterior fontanelle, papilledema, and neurologic findings.

Hearing

Although more frequently occurring in adults with XLH, hearing impairment may begin in childhood, with current reports indicating up to 8% of children are affected (18). Hearing loss is most often asymmetric and sensorineural in nature, although conductive defects have been reported (63). The underlying etiology is not well understood; however, the suggested mechanisms include endolymphatic hydrops, osteomalacia of the ossicles, osteosclerosis of the petrous bone (64), and osteomalacia of the otic capsule (65). Tinnitus has also been reported to occur more frequently in children with XLH (18).

Quality of Life

The health-related quality of life (HRQoL) of patients with XLH is reported to be inferior to that of the general population as well as those affected by other chronic diseases. In a study of 21 children with XLH using the EuroQol-5 dimensions instrument, HRQoL measures were worse than that of the general Spanish population (66). Particular areas of concern were related to mobility (61.9%), washing or dressing (9.52%), and performance of usual activities (33.3%) (66). Moderate pain or discomfort was present (61.9%) as was moderate anxiety

or depression (23.8%) (66). Contributing factors may include diagnostic delay, treatment difficulties, poor psychosocial support, and poor social integration (66). Similar findings were reported among 14 Japanese and Korean children with XLH (67). Despite oral phosphate and active vitamin D use, short stature, gait abnormalities, dental conditions, and decreased physical function were reported to persist (67). Another study from North America and France reported similar findings via caregiver surveys (18). Studies examining the impact of burosumab therapy on quality of life (QoL) in children and adolescents using validated QoL questionnaires are limited. In the RCT of burosumab compared to conventional therapy, pain interference, physical function, mobility, and fatigue scores improved with burosumab after 40 and 64 weeks, whereas little change occurred with continuation of conventional therapy (44).

MONITORING RECOMMENDATIONS—FOLLOW-UP (GRADEd) (Fig. 3)

Follow-up assessment in all children from infancy to adolescence is carried out **every 3-6 months unless otherwise specified**

We Suggest (weak recommendations, very low certainty evidence)*.

1. Standing height (recumbent length in children \leq 2 years), weight, head circumference, and blood pressure measurements expressed as age- and sex-matched percentile or Z-score
2. Physical examination for skeletal deformities (eg, rickets, genu varum, genu valgum, tibial torsion, spinal lordosis/kyphosis/scoliosis) in children \geq 6 months old
3. Growth velocity measurements for children up until the time of epiphyseal fusion (adult height attainment)
4. Documentation of dental infections or maxillo-facial cellulitis history

5. Measurements of serum phosphorus, calcium corrected for albumin or ionized calcium, ALP, kidney function (creatinine, eGFR), PTH, spot urine calcium/creatinine, morning spot urine phosphorus/creatinine (*specimens preferred to be morning, fasting for at least 2-3 hours, with serum and urine samples collected simultaneously or within 2 hours of each other*)
6. Measurements of circulating 25-hydroxyvitamin D, at least once a year**
7. Renal imaging by ultrasound annually, or less frequently to screen for nephrocalcinosis
8. Knee/hand-wrist x-rays to evaluate for rickets or rachitic changes, as clinically indicated.
9. Targeted x-rays to assess for fractures or joint damage, in the presence of localized pain
10. Dental visit in all children \geq 1 year old (after tooth eruption) to prevent and treat dental infections, every 6-12 months

Practices that we suggest to not routinely order (thus considered discretionary) all are weak recommendations with very low certainty.

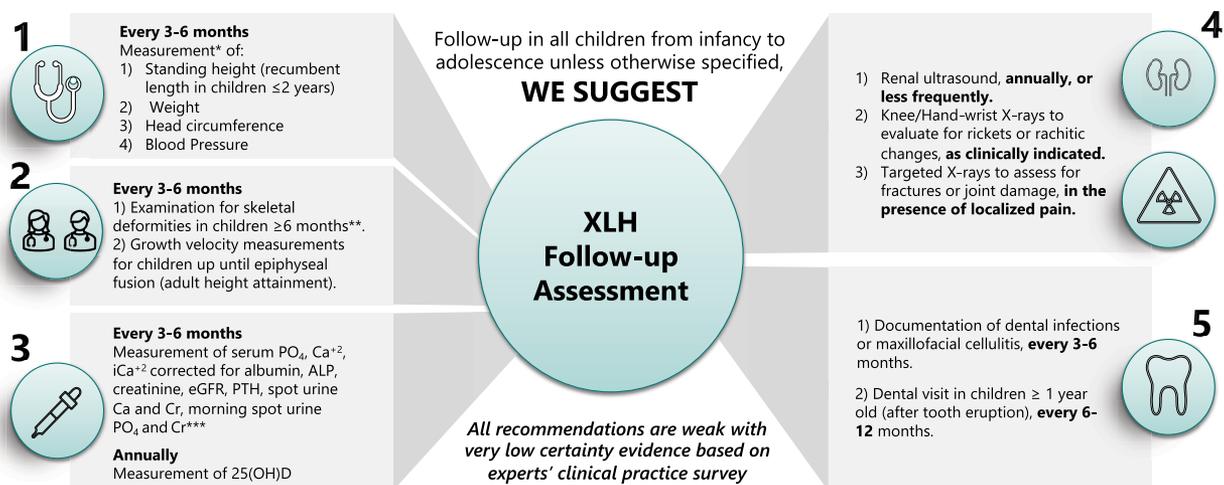
1. Mobility assessment with 6MWT, unless symptoms are present
2. Routine QoL assessment
3. Routine fundoscopy examination in children \leq 2 years old
4. Routine 24-hour urine calcium to creatinine measurements
5. Routine determination of RGI-C
6. Routine BMD measurements in children***

*Based on clinical practice survey with 80% of experts performing the clinical practice in 80% of their patients.

**Ideally at the end of winter for those with seasonal sunlight exposure.

***BMD measurements are not informative for decision making and represent another exposure to radiation in

Monitoring Recommendations in Children (GRADEd)



*All expressed as age- and sex-matched percentile or Z-score.

**Genu varum, genu valgum, tibial torsion, spinal lordosis/kyphosis/scoliosis).

***All specimens preferred to be morning, fasting for at least 2-3 hours, with serum and urine samples drawn simultaneously or within a maximum of 2 hours of each other.

Abbreviations: ALP: alkaline phosphatase; Ca^{+2} : calcium; iCa^{+2} : ionized calcium; Cr: creatinine; PTH: parathyroid hormone; PO_4 : phosphorus; 25(OH)D: 25-hydroxyvitamin D

Figure 3. GRADEd monitoring recommendations for follow-up in children with XLH.

these children and therefore are not recommended.
Abbreviations: ALP, alkaline phosphatase; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; QoL, quality of life; RGI-C, Radiographic Global Impression of Change; 6MWT, 6-minute walk test.

MONITORING RECOMMENDATIONS (NON-GRADED)

The panel proposes

1. Hearing evaluations as part of the periodic assessment.
2. Comprehensive neurologic and fundoscopic examinations in the presence of neurological symptoms such as headache, vomiting, loss of developmental milestones.

How to Treat?

TREATMENT RECOMMENDATIONS* (GRADED)

1. In children 12 months of age and older with XLH, **we recommend** burosumab therapy over conventional therapy (active vitamin D and phosphate salts) (*strong recommendation, moderate certainty*).
2. In children 6-12 months of age with XLH, **we suggest** burosumab therapy over conventional therapy (active vitamin D and phosphate salts) (*conditional recommendation, low certainty*).

* We recognize that there may be limitations to drug therapy accessibility

TREATMENT RECOMMENDATIONS (NON-GRADED)

The panel proposes

1. Commence medical therapy promptly upon confirming XLH diagnosis and hypophosphatemia to optimize outcomes.
2. Treatment is directed at improving radiographic, biochemical and clinical signs of rickets (serum ALP, total or bone-specific), lower limb deformity, physical function, and the optimization of growth by addressing the mineral metabolism abnormalities of XLH.
3. When treating with burosumab, adhere to the recommended starting dose and adjust doses to achieve serum phosphorus levels in the low- to mid-normal (peak) or just below the normal or low-normal (trough) range for age, while avoiding hyperphosphatemia at any point in the dose cycle.
4. Optimal management with burosumab entails dose adjustments based on optimizing serum phosphorus levels for age rather than solely based on weight increases to avoid increasing the risk of hyperphosphatemia.
5. If burosumab is not available, children should be treated with conventional therapy (active vitamin D, usually combined with phosphate salts). Conventional therapy is advised over no treatment.
6. Active vitamin D can be administered with or without phosphate salts, but phosphate salts should not be used as monotherapy.
7. When treating with conventional therapy (active vitamin D with or without phosphate salts), avoid targeting

normal fasting serum phosphorus levels to prevent phosphate overdosing or toxicity.

8. Adjust active vitamin D and oral phosphate therapy with the aim to lower, and to normalize alkaline phosphatase activity, if this can be safely achieved, and promote normal linear growth. However, phosphate doses exceeding 60 mg elemental phosphorus/kg/day are rarely well-tolerated. The active vitamin D dose should be decreased in the presence of persistent hypercalciuria. However, unbalanced increases in the phosphate doses without raising active vitamin D doses increases the risk of sustained hyperparathyroidism.
9. Consider decreasing the phosphate dose or increasing the active vitamin D dose (the latter, in the absence of hypercalciuria/hypercalcemia) if PTH levels are consistently elevated, as phosphate stimulates PTH secretion and calcitriol can suppress PTH.
10. The routine use of recombinant human growth hormone for children with XLH and short stature is not advised due to limited benefit noted in randomized clinical trials.
11. Early involvement of orthopedic surgery is crucial to assess for the necessity, and the timing of, any corrective procedures.
12. In tertiary hyperparathyroidism, multigland involvement is expected. Calcimimetics (ie, cinacalcet) can be used on an off-label basis to decrease PTH level in the setting of hypercalcemic hyperparathyroidism, while ensuring close monitoring of serum calcium in order to avoid hypocalcemia. If hyperparathyroidism and hypercalcemia cannot be controlled, subtotal parathyroidectomy should be considered.
13. Burosumab is contraindicated in chronic kidney disease (eGFR < 30 mL/min), and in acute kidney injury. Cautious use is advised if eGFR is between 30 and 60 mL/min with careful monitoring for hyperphosphatemia and changes in eGFR.
14. If clinic blood pressure measures consistently exceed the 95th percentile (for age and height) confirmation with 24-hour ambulatory blood pressure monitoring or serial home blood pressure measurements is indicated. Treatment should follow current pediatric hypertension recommendations.

Children on Conventional Therapy

Since the 1980s, the usual approach to medical therapy in pediatric XLH has consisted of treatment with oral phosphate salts in combination with an activated vitamin D metabolite (usually calcitriol or alfacalcidol). This conventional therapy approach was more effective than the previously used regimens of high-dose vitamin D (ergocalciferol or cholecalciferol) together with phosphate salts. Moreover, hyperparathyroidism was less frequently seen than with phosphate monotherapy or with high-dose vitamin D. Additionally, the complication of prolonged hypercalcemia from high-dose vitamin D could be avoided. Phosphate salts and active vitamin D treatment are most effective when the phosphate salt is given multiple (usually 4 or more) times per day, spaced to maximize exposure (due to rapid absorption and renal elimination). For active vitamin D, calcitriol (1,25-dihydroxyvitamin D), is usually given twice daily, or alfacalcidol (prodrug) once daily. While calcitriol is more potent than alfacalcidol, the half-life of alfacalcidol is longer. There are no studies comparing the effectiveness of the 2 agents in treating

XLH. Evidence is based mostly on studies conducted in patients with secondary hyperparathyroidism in association with chronic kidney disease, the effective dose of alfacalcidol is 1.5 to 2.0 times that of calcitriol, probably explained by the higher bioavailability of calcitriol (68). Calcitriol doses generally range from 20 to 50 ng/kg/day, alfacalcidol from 25 to 40 ng/kg/day (69, 70) and phosphate salt supplementation is usually given in doses of 20 to 60 mg of elemental phosphorus/kg/day. Active vitamin D monotherapy has been used clinically in XLH, particularly in mild cases; however the greater risk of hypercalciuria with this approach may be a potential challenge as observed in early clinical studies (71). An ongoing clinical trial (NCT03748966) is now evaluating calcitriol as a monotherapy in children and adults with XLH. Further studies are warranted in this area.

Treatment is more effective in addressing skeletal and dental complications when initiated early in the child's course. This improves rachitic growth plate lesions and skeletal deformities, with some improvement in stature. Nevertheless, conventional therapy usually does not result in complete healing of rickets, prevention or full correction of lower limb deformity, or normalization of growth, and orthopedic surgical intervention is frequently required. The care of children with XLH is challenging and based on a paucity of data, and as such, many other groups have provided guidance on the diagnosis and management (70, 72–74).

Conventional therapy requires frequent laboratory monitoring for toxicity and efficacy, and appropriate dose adjustments (see accompanying monitoring manuscript). Normalization of serum phosphorus for age is never a treatment goal using the conventional treatment regimen due to risk of toxicities (including hyperparathyroidism and worsening nephrocalcinosis). It is important to focus on clinical outcomes (radiographic signs of rickets, lower limb deformity, physical function, and growth). Decreasing and, if possible, normalization of ALP is, however, important as it indicates improved bone mineralization and healing of the rickets/osteomalacia. It is also advised to provide adequate active vitamin D with the phosphate salts to avoid the complication of hyperparathyroidism. The most common complications of conventional therapy include gastrointestinal side effects, hypercalciuria, nephrocalcinosis, and hyperparathyroidism. Nephrocalcinosis is frequent with or without detectable hypercalciuria (51).

Children on Burosumab

The discovery that excess FGF23 plays a major role in the excess renal loss of phosphate led to the development of burosumab, a humanized anti-FGF23 antibody. These developments brought forth a more targeted therapeutic approach for XLH. In pediatric studies, an every-2-weeks regimen of subcutaneously administered burosumab resulted in more rapid normalization of ALP activity, improved renal phosphate reabsorption, and more consistently improved serum phosphorus throughout the dose cycle compared to every-4-weeks dosing (14) or to conventional therapy (44). The favorable biochemical parameters were reflected in improved clinical features of the disease (rickets, lower limb deformities) to a greater extent than conventional therapy, without the burdensome regimen or complication profile of phosphate salts and active vitamin D (44). Real world data have been confirmatory of these earlier studies and have indicated patient preference for burosumab injections every 2 weeks over multiple daily doses of conventional therapy (75).

Childhood burosumab dosing recommendations vary by regulatory agency, beginning with 0.4 to 0.8 mg/kg every 2 weeks; however, titration is often necessary to correct hypophosphatemia, and some children require doses that are below or exceed this range in order to maintain normal phosphorus and optimize outcomes. Maximum doses accessible may vary by country; US Food and Drug Administration (FDA)-approved doses in children extend up to 2 mg/kg (maximum 90 mg) every 2 weeks.

Local site injection reactions such as urticaria are common but appear minor based on available data, as they did not result in drug discontinuation in the pivotal trial (44). A potential side effect based on the mechanism of blocking FGF23, hyperphosphatemia, may rarely occur, as was described in some patients in the adult trial (37); this requires an immediate dose adjustment. The bulk of the current evidence suggests that the risks of hyperparathyroidism and nephrocalcinosis may be less with burosumab than with conventional therapy, although that experience is not universal (76). Decreases in urinary calcium excretion with burosumab compared to conventional therapy further supports the possibility of a decreased risk of nephrocalcinosis (77).

Nevertheless, burosumab is expensive and not universally available. There is considerable international variability with respect to regulatory approvals for, and market access to, burosumab (based on age of patient and in some cases disease severity). Even where regulatory approval exists, there is disparate public funding across age ranges (with some, but not all, countries funding to as low as 6 months of age or extending coverage to adults). Gaps in burosumab availability remain an unmet need and arguably an important global social equity issue.

Role of Recombinant Human Growth Hormone

Short stature is common among patients with XLH, with a disproportionate preservation of trunk height as compared to substantially altered total height (78). Recombinant human growth hormone (rhGH) has been used in several observational studies to attempt to improve the final height in XLH; with some noting increased growth rates (79, 80). However, in a 3-year randomized trial, despite apparent increased growth rate, the treated groups did not differ, and the skeletal disproportion is not ameliorated (81). Moreover, near-final height did not differ between rhGH-treated patients and controls (82). Therefore, we do not recommend routine use of rhGH in short children with XLH.

Transitioning Children to Adult Care

It is important to empower the young adult with a chronic condition during the transition period. Information on the condition, available treatment options, patient groups, the local medical system and necessary specialists involved in future care need to be discussed before the transfer to the adult health care system. Follow-up appointments with endocrinology/nephrology, orthopedics, physiatry, physical therapy, neurosurgery, occupational therapy, ENT, audiology, dentistry and other specialties should be organized as appropriate for the individual to ensure continuation of care (83–85).

Although many patients undergo a trial off conventional therapy after reaching adulthood (or switch to monotherapy with active vitamin D), the best approach and duration of therapy is not clear. Likewise, the best approach following treatment during childhood with burosumab is also not clear. To optimize peak bone mass, medical therapy should be continued

for at least several years following epiphyseal closure. In some geographic areas, burosumab is not available for adults, and no trial has adequately assessed continuing vs stopping burosumab during the adolescent transition, switching from burosumab to conventional therapy at this time point, or the best timing for changing from pediatric burosumab dosing every 2 weeks to adult dosing every 4 weeks. It might be beneficial to continue burosumab for several years after cessation of growth to optimize bone accrual and mineralization, but this has not been studied. If continuing burosumab in adulthood, it is reasonable to consider transitioning to monthly dosing within 1 to 2 years following fusion of the growth plates. However, anecdotally some young adults note more bone pain during accompanying hypophosphatemia after stopping burosumab or even after switching from dosing every 2 weeks to dosing every 4 weeks. Fundamentally, it is important to recognize that even following treatment during the pediatric years, the osteomalacia of XLH persists or recurs in adulthood, as confirmed by trans-iliac histomorphometry (86).

Orthopedic and Related Surgical Procedures

Surgical management of the lower extremities in XLH ranges from guided growth (a minimally invasive procedure in which a tension-band plate or screw is applied to the epiphysis on the longer side of a limb to inhibit growth and slowly straighten the limb over time in patients with less deformity and open physes) to corrective osteotomies (in severe 3-dimensional deformities or with closed physes). The rate of correction after guided growth surgery is slower in patients with XLH when compared to other deforming disorders. Similarly, patients with XLH are more likely to require secondary procedures and have a lower rate of achieving neutral mechanical alignment (50, 87, 88). However, recent analysis of the burosumab clinical trial suggests that the drug's disease-modifying benefits may halt the progression or even improve the lower limb deformities associated with conventional therapy and minimize the need for surgery, but further investigation is needed (89). An increased incidence of scoliosis in XLH has not been described; however, given the impact of XLH on bone's mechanical properties, careful observation of spinal alignment throughout growth, including the development of scoliosis, is advised (89). Although studies have not systematically compared medical treatment modalities, medical therapy for XLH is likely to be important to orthopedic surgical outcomes.

Physical Therapy

Lower limb deformities, bone pain, disproportionate stature, early fatigue, and muscle weakness present functional challenges for children with XLH (45, 46). Physical therapy complements medical and surgical care by assessing bone and joint alignment, pain, strength, and gross motor skills, and intervention directs therapy toward strengthening, range of motion, motor skills, and daily function. Strategic goals include prevention of falls, modulation of loading and torsion, and activity participation, as to support overall QoL. Examination includes assessment of lower extremity bowing and torsion, foot progression angles, and walking/running patterns (90, 91). Power and mechanics are assessed via jumping and hopping.

Minimal intervention such as clinic-based coaching with education and reassurance may be sufficient for children treated early with limited impairment (92). Orthoses are

generally not indicated as they tend to increase in-toeing. Bulky footwear tends to increase tripping.

For untreated or late-treated children affected by pain and deformity, activity modification, protective strategies, and pain reduction are particularly important. For those undergoing alignment surgery, postoperative strengthening, functional mobility, gait training, and use of assistive devices come into play (87, 93).

Caution with higher-impact (contact sports, running, jumping) and higher-torsion (gymnastics, wrestling, tennis) activities, paired with lesser-impact activities (swimming, cycling, climbing, yoga, dance, martial arts), is prudent for lifespan health and overall QoL.

Dental and Oral Complications

DENTAL RECOMMENDATIONS (NON-GRADED)

The panel proposes

1. Early treatment in children with either (active vitamin D and phosphate salts, or burosumab) is indicated to improve tooth mineralization and reduce the number of dental infections.
2. Performing a thorough clinical and radiological dental investigation searching for spontaneous pulp infection (abscess, tooth color changes, fistula, swelling, cellulitis, pain, periapical bone loss).
3. Performing cone-beam computed tomography assessment in selected cases to better evaluate suspected dental anomalies or the presence and extent of dento-alveolar infection.
4. Sealing pits and fissures with flowable resin composite on both temporary and permanent teeth as soon and as frequently as required is advised.
5. Optimizing medical treatment of XLH with either (active vitamin D and phosphate salts, or burosumab) if orthodontic treatment is required.

Dental Complications in Children

Dental complications are common morbidities in patients with XLH (70, 94–97) that alter QoL (98–100). Practitioners not familiar with XLH may not recognize the source of these issues (70, 94, 95). Dental enamel appears clinically normal (101, 102) but is thinner, with microscopic cracks (96, 103, 104). Dentin mineralization is severely impaired in both primary and permanent teeth (96, 101–103, 105), with low mineral density, unmineralized spaces, enlarged predentin, and consequently, enlarged pulp chambers with prominent pulp horns (103, 104). These features explain the high susceptibility of XLH patients to spontaneous pulp necrosis (3, 96, 103), which may manifest as dental abscesses in teeth that appear healthy (103, 106), or, less frequently, by maxillofacial cellulitis. Spontaneous pulp necrosis may even occur in the absence of an antecedent dental abscess or regional cellulitis. In some cases, spontaneous pulp necrosis may occur with no immediate clinical manifestations, such as dental abscess or regional cellulitis, and thus is detectable only radiographically. Malocclusions can be present (107).

Prevention and Management

A dentist must be part of the multidisciplinary team caring for patients with XLH (1, 70, 94, 95). Dental visits are

recommended in children every 6 months. Sealing identified pits and fissures of both temporary and permanent teeth is advised (70, 108). A thorough clinical examination should be performed to search for pulp necrosis. Bitewings and/or periapical radiographs, orthopantomogram (after 6 years of age) or cone-beam computed tomography can be performed based on clinical needs (70, 109–111). Optimized general medical treatment of XLH should be established before initiation of any necessary orthodontic treatment.

Comparative Effects of Burosumab and Conventional Therapy on Dental Complications

Early conventional therapy with good compliance improves dentin and potentially cementum mineralization (103), and reduces dental infections in children (4, 112). While an RCT comparing conventional therapy and burosumab in children showed more dental infections in the burosumab group, a post hoc analysis showed fewer infections in children treated with burosumab before age 5 (113). In a prospective case-control study involving 10 children treated with burosumab for 3 years, enlarged pulp chambers persisted but only one child developed a dental abscess (114). A single-center, retrospective study showed positive outcomes on the incidence of dental abscess in the 33 children treated with burosumab vs the 38 treated with conventional therapy (115).

Relation to Previous Guidelines

Our recommendations were developed by an IWG of experts in XLH management and GRADE methodology. The recommendations are categorized as strong, weak, or conditional, depending on the level of evidence. We conducted two systematic reviews to inform our treatment recommendations (5). To date, there are 3 published guidelines (70, 74, 116) and 4 consensus statements (3 of which are regional) (72, 73, 117, 118). Our GRADEd monitoring recommendations were based on a rigorous expert clinical practice survey, where consensus was defined as parameters practiced by 80% of respondents 80% of the time. In comparison, some guidelines relied on narrative reviews, modified Delphi methods, or expert meetings (72–74, 117). Our guidelines are the only international guidelines that followed the fundamental principles of GRADE methodology.

Beyond methodology, several key clinical recommendations differentiate our guidelines from others. For instance, we do not recommend the use of rhGH for short stature in children with XLH, due to insufficient evidence, whereas other guidelines consider its use for short stature (70). Although most guidelines consistently recommend medical therapy in children once the diagnosis of XLH is confirmed, there are variations in the strength of the recommendations.

Our guidelines also include a list of tests that are not suggested for routine use in children, including the 6-minute walking test (6MWT) and bone mineral density (BMD) assessment. This recommendation is based on consensus from a clinical practice survey of our expert panel. We ensured that our recommendations are practical and avoided the use of tools not validated in XLH or those primarily used in clinical research.

Limitations

Some authorities recommend an external panel using a Delphi process to further enhance the trustworthiness of a guideline.

Our guideline is limited in that it did not conduct such a process. We did, however, conduct a detailed expert survey (being published separately) regarding management practices, which did inform this guideline. Items from that survey that indicated that $\geq 80\%$ of providers responding performed the evaluation in $\geq 80\%$ of their XLH patients, were incorporated into the guidelines. We also obtained external validation by sharing the guidelines with numerous national and international societies involved in the care of individuals with XLH and other rare bone diseases. Their endorsements were obtained, and their feedback was incorporated into the final manuscript. We did not have representation from Africa or Australia, with few representatives from Asia and South America. These limitations, however, are not uncommon across most consensus documents on the management of rare diseases.

Summary

The recommendations and guidelines outlined in this report for the evaluation and management of XLH in children represent a comprehensive assessment utilizing both GRADE methodology as the basis for 2 recommendations and a clinical practice survey informing monitoring recommendations, alongside narrative reviews to formulate non-GRADEd recommendations. These global guidelines underwent a rigorous process, incorporating 2 systematic reviews informing the GRADEd recommendations, as fully described in a separate manuscript (5).

Treatment recommendations were developed for children aged 6 months and older, ensuring comprehensive coverage across pediatric age groups. Monitoring recommendations encompassed both the initial assessment of suspected XLH patients and ongoing monitoring of existing patients, from infancy to adolescence. The guidelines also emphasized dental complications, providing recommendations for prevention and management strategies, as well as orthopedic and rehabilitation management. We intend to update these guidelines as additional data become available.

Research Agenda

Going forward, many questions remain unanswered that would add to our understanding of optimal approaches to management of XLH in children. First, it remains unclear at this time the extent to which burosumab therapy in childhood can mitigate disease-related comorbidities over the longer term, including dental abscesses, short stature, hearing impairment, enthesopathy, osteoarthritis, spinal stenosis, lower limb deformity, and the need for orthopedic intervention. Secondly, whether burosumab initiation as soon as hypophosphatemia is confirmed in infancy portends a more favorable prognosis than starting therapy at 1 year of age or older remains unknown. For some disease-related comorbidities, such as hearing loss, Chiari 1 malformation, syringomyelia and enthesopathy, a greater understanding of the precise pathobiology in order to refine treatment strategies that will minimize their impact on patient QoL is warranted. Going forward, well-designed clinical trials and long-term registries which seek the highest quality of evidence will be needed to fully understand the natural history of XLH and the extent to which effective surgical and medical therapies can support patients with XLH to live their best lives. Finally, understanding the global unmet need, including access to XLH clinical

experts, multidisciplinary services and state-of-the-art treatments in underdeveloped countries, remains a pressing social responsibility of the XLH stakeholder community.

Endorsement

To date, this manuscript has been endorsed by the following societies: the American Society for Bone and Mineral Research (ASBMR), the Canadian Society of Endocrinology and Metabolism (CSEM), the Canadian XLH Network (patient group), the Chilean Society of Osteology and Mineral Metabolism (SCHOMM), the Endocrine Society, the French Dental Association, the International Society of Children's Bone Health (ISCBH), the Irish Endocrine Society (IES), the Japanese Society for Bone and Mineral Research (JSBMR), the Kuwait Academy of Rare Diseases (KARD), the Pediatric Endocrine Society (PES), and XLH Denmark (patient group).

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Data Availability

The data supporting the findings in this study are openly available in PubMed, EMBASE, and the Cochrane databases.

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