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Reports and Recommendations

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

Aliya A. Khan,[1] Dalal S. Ali,[1] Natasha M. Appelman-Dijkstra,[2] Thomas O. Carpenter,[3] Catherine Chaussain,[4,5,6] Erik A. Imel,[7] Suzanne M. Jan de Beur,[8] Pablo Florenzano,[9] Hajar Abu Alrob,[10] Rana Aldabagh,[11] R. Todd Alexander,[12] Farah Alsarraf,[1] Signe Sparre Beck-Nielsen,[13,14] Martin Biosse-Duplan,[4,5,6] Martine Cohen-Solal,[15] Rachel K. Crowley,[16] Karel Dandurand,[17] Guido Filler,[18] Lisa Friedlander,[4] Seiji Fukumoto,[19] Claudia Gagnon,[20,21] Paul Goodyer,[22] Corinna Grasemann,[23] Chelsey Grimbly,[24,25] Salma Hussein,[1] Muhammad K. Javaid,[26] Sarah Khan,[27] Aneal Khan,[28] Anna Lehman,[29] Willem F. Lems,[30] E. Michael Lewiecki,[31] Ciara McDonnell,[32,33] Reza D. Mirza,[10] Emmett Morgante,[34] Archibald Morrison,[35] Anthony A. Portale,[36] Yumie Rhee,[37] Eric T. Rush,[38,39] Heide Siggelkow,[40,41] Sotirios Tetradis,[42] Laura Tosi,[43] Leanne M. Ward,[44] Gordon Guyatt,[10,45,46] and Maria Luisa Brandi[47]

[1]Division of Endocrinology and Metabolism, McMaster University, Hamilton, ON L8S 4L8, Canada
[2]Department of Internal Medicine, Division of Endocrinology, Center for Bone Quality, Leiden University Medical Center, Leiden 2300 ZA, the Netherlands
[3]Departments of Pediatrics (Endocrinology), and Orthopaedics and Rehabilitation, Yale University School of Medicine, New Haven, CT 06520, USA
[4]Department of Oral Medicine, Faculty of Dentistry, UMR 1333, Université Paris Cité, Paris 75006, France
[5]Institut Imagine, INSERM 1163, 75015 Paris, France
[6]Department of Oral Medicine, APHP, Paris 75006, France
[7]Department of Medicine and Pediatrics, Endocrinology, Indiana University School of Medicine, Indianapolis, IN 46202, USA
[8]Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA 22903, USA
[9]Department of Endocrinology, School of Medicine Pontificia Universidad Católica de Chile, Santiago 8320165, Región Metropolitana, Chile
[10]Department of Health Research Methods, Evidence, and Impact at McMaster University, Hamilton, ON L8S 4L8, Canada
[11]Faculty of Dentistry, University of Toronto, Toronto, ON M5G 2L3, Canada
[12]Faculty of Medicine & Dentistry, The University of Alberta, Edmonton, AB T6G 2R3, Canada
[13]Centre for Rare Diseases, Aarhus University Hospital, Aarhus N 8200, Denmark
[14]Department of Clinical Medicine, Aarhus University, Aarhus N 8200, Denmark
[15]Department of Rheumatology and reference center for Rare Bone Diseases, hopital Lariboisiere, Paris 75006, France
[16]Rare Disease Clinical Trial Network, University College Dublin, Dublin 4, D04 T6F4, Ireland
[17]Division of Internal Medicine, Endocrinology Division, Université de Sherbrooke, Sherbrooke, QC J1H 5N4, Canada
[18]London Health Sciences Centre, Children's Hospital of Western Ontario, London, ON N6A 3K7, Canada
[19]Department of Medicine, Tamaki-Aozora Hospital, Tokushima 779-3125, Japan
[20]Endocrinology and Nephrology Axis, CHU de Québec-Université Laval Research Centre, Québec, QC G1V 4G2, Canada
[21]Department of Medicine, Université Laval, Québec, QC G1V 0A6, Canada
[22]Research Institute of the McGill University Health Centre, Montreal, QC H3H 2L9, Canada
[23]Department of Pediatrics, Division of Rare Diseases, Katholisches Klinikum Bochum and Ruhr-University Bochum, 44791 Bochum, Germany
[24]Department of Pediatrics, University of Alberta, Edmonton, AB T6G 2R3, Canada
[25]Women and Children's Health Research Institute, Edmonton, AB T6G 1C9, Canada
[26]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford OX3 7HE, UK
[27]Trillium Health Partners, University of Toronto, Toronto, ON L5M 2N1, Canada
[28]M.A.G.I.C. Clinic (Metabolics and Genetics in Canada), Calgary, AB T2E 7Z4, Canada
[29]Department of Medical Genetics, University of British Columbia, Vancouver, BC V6T 1Z4, Canada
[30]Department of Rheumatology, Amsterdam UMC, Amsterdam 1105 AZ, the Netherlands
[31]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM 87106, USA
[32]Department of Pediatric Endocrinology & Diabetes, Children's Health Ireland, Dublin D12 N512, Ireland
[33]Department of Paediatrics, School of Medicine, University of Dublin, Trinity College, Dublin D02 PN40, Ireland

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[34]Department of Kinesiology, University of Waterloo, Waterloo, ON N2L 3G1, Canada
[35]Citadel Oral and Facial Surgery, Halifax, NS B3L 4H7, Canada
[36]Department of Pediatrics, University of California San Francisco, San Francisco, CA 94115, USA
[37]Endocrine Research Institute, Department of Internal Medicine, Yonsei University College of Medicine, Seoul 03722, Korea
[38]Division of Clinical Genetics, Children's Mercy Kansas City, Kansas City, MO 64108, USA
[39]Department of Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, MO 64108-2792, USA
[40]Department of Trauma, Orthopedics and Reconstructive Surgery, University Medical Center Goettingen, 37075 Goettingen, Germany
[41]MVZ Endokrinologikum Goettingen, 37075 Goettingen, Germany
[42]Division of Diagnostic and Surgical Sciences, UCLA School of Dentistry, Los Angeles, CA 90095, USA
[43]Department of Orthopedics, George Washington University School of Medicine and Health Sciences, Washington, DC 20052, USA
[44]Children's Hospital of Eastern Ontario, Department of Pediatrics, University of Ottawa, Ottawa, ON K1H 8L1, Canada
[45]Department of Medicine, McMaster University, Hamilton, ON L8S 4L8, Canada
[46]MAGIC Evidence Ecosystem Foundation [www.magicevidence.org], Oslo 0456, Norway
[47]Institute of Endocrine and Metabolic Sciences, Vita-Salute San Raffaele University and IRCCS, Milan 20132, Italy

Correspondence: Aliya Khan, MD, FRCPC, FACP, FACE, McMaster University, 223-3075 Hospital Gate, Oakville, ON L8M 1M1, Canada.
Email: aliya@mcmaster.ca, draliyakhan@gmail.com

Abstract

Purpose: An international working group (IWG) consisting of experts in X-linked hypophosphatemia (XLH) developed global guidelines providing a comprehensive, evidence-based approach to XLH diagnosis, management, and monitoring.

Methods: The IWG, consisting of 43 members as well as methodologists and a patient partner, conducted 2 systematic reviews (SRs) and narrative reviews to address key areas. The SRs addressed the impact of burosumab compared to conventional therapy (phosphate and active vitamin D) or no therapy on patient-important outcomes in adults. They also evaluated conventional therapy compared to no therapy. GRADE methodology was applied to evaluate the certainty of evidence. Non-GRADED recommendations were made in the presence of insufficient evidence to conduct SRs. These guidelines have been reviewed and endorsed by several medical and patient societies and organizations.

Results: The diagnosis of XLH is based on integrating clinical evaluation, laboratory findings confirming renal phosphate wasting (following exclusion of conditions mimicking XLH), and skeletal imaging. Fibroblast growth factor 23 measurement and DNA analysis are of value in the diagnosis, if available. Pathogenic or likely pathogenic variants in the *PHEX* gene are confirmatory but not necessary for the diagnosis. Management requires a multidisciplinary team knowledgeable and experienced in XLH. Effective medical therapy with burosumab can improve fracture and pseudofracture healing.

Main Conclusion: In adults with XLH and fractures or pseudofractures, burosumab is recommended over no therapy (strong recommendation, GRADEd). Additionally, burosumab is suggested as the preferred treatment compared to conventional therapy (conditional recommendation, GRADEd) in the absence of fractures or pseudofractures. If burosumab is not available, symptomatic adults should be treated with conventional therapy (Non-GRADEd recommendation).

Key Words: X-linked hypophosphatemia (XLH), clinical practice guidelines, consensus, adult XLH

Abbreviations: 1,25(OH)2D, 1,25-dihydroxyvitamin D; aBMD, areal bone mineral density; AD, autosomal dominant; ALP, alkaline phosphatase; AR, autosomal recessive; BsALP, bone-specific alkaline phosphatase; CKD, chronic kidney disease; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HRQoL, health-related quality of life; IWG, international working group; MSK, musculoskeletal; PHEX, phosphate regulating endopeptidase homolog X-linked (gene); PTH, parathyroid hormone; QoL, quality of life; RCT, randomized controlled trial; SR; systematic review; TmP/GFR tubular maximum phosphate reabsorption adjusted for glomerular filtration rate; VUS, variant of uncertain 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.

X-linked hypophosphatemia (XLH; OMIM 307800), is a rare genetic disorder caused by inactivating variants in the

phosphate regulating gene with homology to endopeptidases (*PHEX*) gene. This results in excess synthesis and secretion of fibroblast growth factor 23 (FGF23), which impairs proximal renal phosphate reabsorption causing renal phosphate wasting and hypophosphatemia. Excess FGF23 also reduces the 1-α hydroxylation of 25-hydroxyvitamin D (25(OH)D) to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) and increases catabolism of $1,25(OH)_2D$ by the upregulation of 24-hydroxylase. These effects lead to decreased absorption of phosphate from the bowel (1). Currently, there is limited data on the natural history of XLH as well as long-term outcomes; however, the burden of disease observed in the adult patient population suggests that late diagnosis and management are associated with adverse outcomes (2, 3). Adults present with osteomalacia, experience chronic musculoskeletal pain, lower limb deformity, fractures, pseudofractures, dental complications, fatigue, and difficulties with mobility and impaired physical function. Medical management includes conventional therapy with phosphate and active vitamin D, and more recently, burosumab (recombinant human IgG1 monoclonal antibody to FGF23) has become available (4).

The pivotal trial in adults comparing burosumab to placebo has demonstrated that burosumab enhanced fracture and pseudofracture healing by 16.8-fold compared to placebo ($P < .001$) (4). In this randomized controlled trial (RCT) burosumab demonstrated a significant reduction in stiffness in comparison to placebo (4). In asymptomatic adult patients with XLH, medical therapy (with either burosumab or phosphate and active vitamin D) is individualized based on symptoms as well as comorbidity.

Methodology

The recommendations in these guidelines are based on 2 systematic reviews (SRs) and an expert panel practice survey, in addition to a narrative review of the literature. The guidelines employed a rigorous approach, 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 (5), and the SRs were preregistered with PROSPERO.

The GRADEd treatment recommendations followed a structured approach, encompassing the formulation of questions in the patient/intervention/comparator/outcome (PICO) format (6), conducting SRs, and rating the quality of evidence in "summary of findings tables" addressing patient-important outcomes (7). The recommendations were classified as strong or weak with a description of the quality of evidence (8, 9), patients' values and preferences were taken into consideration for all 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 panelists. The phrase "*the panel proposes*" was used when presenting non-graded recommendations.

The GRADEd monitoring recommendations are supported by very low-quality evidence and were derived from a detailed expert practice survey. A threshold of 80% agreement among the surveyed experts was chosen as the necessary level to recommend each clinical practice. More details are presented in an accompanying manuscript describing monitoring guidelines for XLH (citation pending publication).

HOW TO DIAGNOSE?

Diagnosis Recommendations in Adults (non-GRADEd)

The Panel Proposes

1. The panel proposes that the diagnosis of XLH be made in the presence of chronic hypophosphatemia in the absence of other conditions resulting in renal phosphate wasting. The diagnosis is supported by an X-linked inheritance pattern (see Fig. 1).

Initial assessment recommendations (GRADEd) (Fig. 2)

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

1. Obtaining a history that includes documentation of XLH in the family, or an X-linked dominant inheritance pattern of hypophosphatemia; fractures or pseudofractures; and dental abscesses and/or periodontitis
2. Standing height, weight, and BMI measurements
3. Blood pressure measurements
4. Musculoskeletal examination for bony tenderness and range of motion
5. Measurements of serum phosphorus, calcium corrected for albumin, ALP, 25-hydroxyvitamin D, kidney function (creatinine, eGFR), TmP/GFR, PTH, 24-hour urine calcium and creatinine (or spot urine calcium and creatinine), 24-hour urine phosphorus and creatinine
6. Genetic testing for hypophosphatemia-associated genes, including *PHEX*
7. Baseline BMD assessment**
8. Baseline dental assessment with periapical x-rays or orthopantomogram to screen for enlarged pulp chambers, pulp necrosis, and periapical bone loss

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

**Despite DXA limitations in XLH, BMD assessment may be of value in adults with skeletal mineralization abnormalities. In such individuals, serial assessment may be of value in the presence of hypogonadism or other conditions which can affect bone density, such as superimposed postmenopausal osteoporosis.

Abbreviations: ALP, alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; PHEX gene, phosphate regulating endopeptidase homolog X-linked gene; PTH, parathyroid hormone; TmP/GFR, tubular maximum phosphate reabsorption adjusted for glomerular filtration rate.

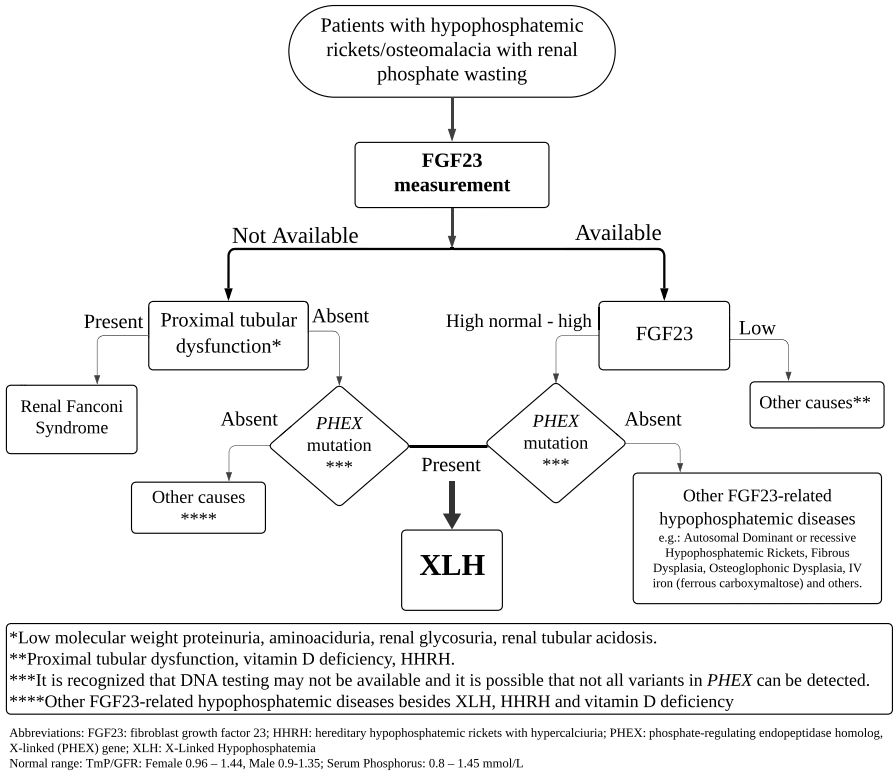


Figure 1. XLH diagnosis algorithm.

INITIAL ASSESSMENT RECOMMENDATIONS (NON-GRADEd)

The Panel Proposes

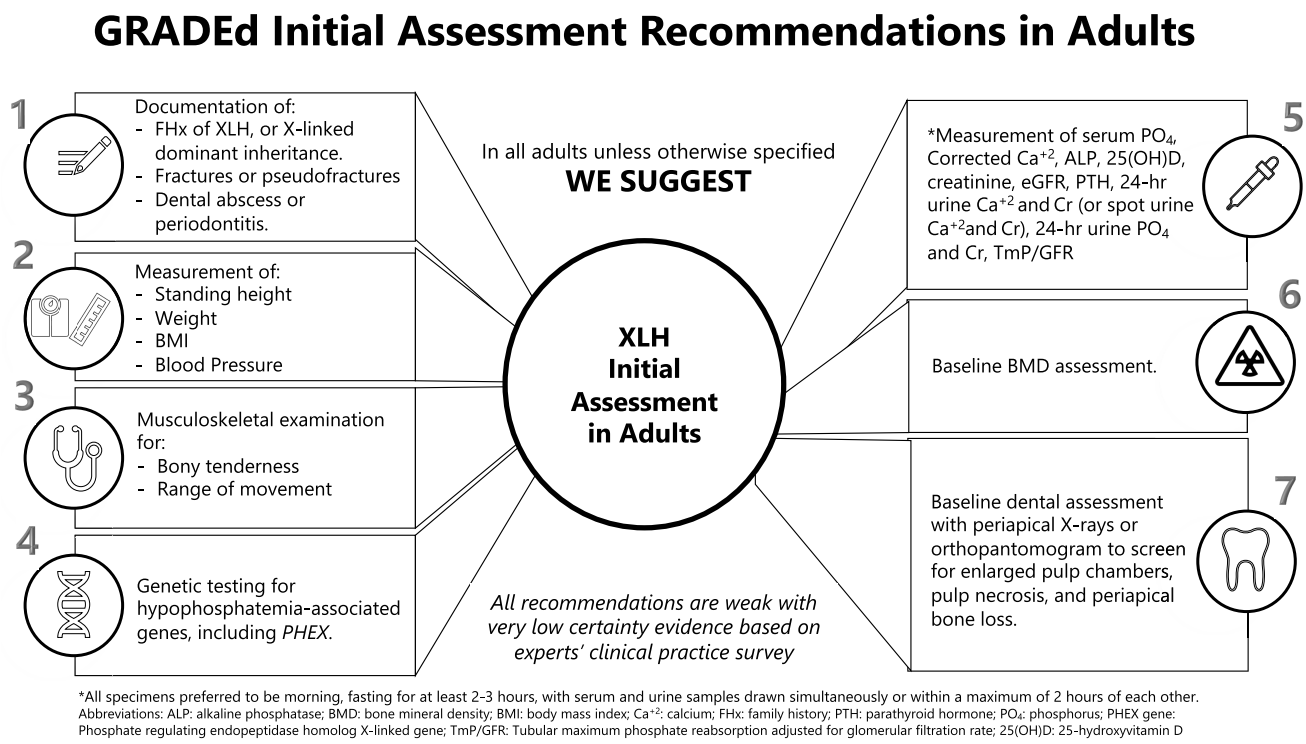
1. At the initial assessment of an adult with XLH, a skeletal survey using plain x-rays is advised to detect asymptomatic pseudofractures. Bone scintigraphy may be used to further evaluate abnormalities if initial radiographs are inconclusive.
2. Evaluation of other possible causes of hypophosphatemia considering the differential (see Fig. 3).

Clinical manifestations, biochemical and radiographic evaluation. In adulthood, XLH is characterized by bone and joint pain, osteomalacia-related fractures or pseudofractures, early joint damage, enthesopathies, muscle weakness, lower limbs deformities, poor dental health, and hearing loss (Table 1) (3, 10). Adults with XLH experience progressive functional limitations, including stiffness and chronic pain as they age. This influences all spheres of quality of life (QoL), including work, travel, physical and mental health, as well as social and family life (10).

The key laboratory finding of XLH is persistently low fasting serum phosphorus. Calcium and parathyroid hormone (PTH) levels are usually normal, although PTH levels may be elevated in XLH. High doses of phosphate therapy contribute to further rises in PTH, leading to secondary and tertiary hyperparathyroidism (11-13). The $1,25(OH)_2D$ level may be low or inappropriately normal, alkaline phosphatase (ALP) may be high or normal, FGF23 levels may be high or inappropriately normal, and bone-specific ALP (BsALP) is usually normal or elevated reflecting the degree of osteomalacia present. The tubular maximum phosphate reabsorption adjusted for glomerular filtration rate (TmP/GFR) is calculated using a fasting second void or 2-hour morning urine specimen with concurrent measurement of phosphorus and creatinine in the serum and urine; a low value is seen with renal phosphate wasting (14). Exclusion of other causes of renal phosphate wasting is required to confirm the diagnosis of XLH (Table 2) (15, 16).

Radiographic manifestations of XLH in adults may include the presence of osteomalacia-related fractures or pseudofractures, which are frequently present at sites of high mechanical stress. In addition, imaging is helpful in identifying early degenerative disc disease involving the spine as well as joint damage of the hips and knees characterized by syndesmophytes on the joint margins. Bone proliferation may occur at sites of ligament attachments, characterized as enthesopathies, or calcification in spinal ligaments (2, 23), and can in severe cases lead to spinal stenosis.

Role of genetic testing. XLH is confirmed by identification of a pathogenic or likely pathogenic *PHEX* variant when an X-linked dominant inheritance pattern is not evident in the family (24-26). In the case of an unknown genetic variant in the family, genetic testing may involve any form of testing that sequences the *PHEX* gene (single-gene sequencing, gene panels, whole-exome sequencing, and whole-genome sequencing) and the finding of a pathogenic or likely pathogenic variant in the *PHEX* gene can support the diagnosis of XLH. About one-third of patients do not have a recognized family history (27-30). Conventional *PHEX* gene sequencing may not reveal pathogenic mosaicism, deep intronic variants, chromosomal rearrangements, or other hereditary disorders



*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; BMD: bone mineral density; BMI: body mass index; Ca^{+2}: calcium; FHx: family history; PTH: parathyroid hormone; PO_4: phosphorus; PHEX gene: Phosphate regulating endopeptidase homolog X-linked gene; TmP/GFR: Tubular maximum phosphate reabsorption adjusted for glomerular filtration rate; 25(OH)D: 25-hydroxyvitamin D

Figure 2. GRADEd initial assessment recommendations in adults with XLH.

of hypophosphatemia due to variants in *CYP27B1* (autosomal-recessive [AR] vitamin D dependent rickets type 1), *CYP2R1* (AR deficient vitamin D 25-hydroxylation), *DMP1* and *ENPP1* (AR hypophosphatemic rickets), *FAM20C* (AR Raine syndrome), *FGF23* (autosomal-dominant [AD] hypophosphatemic rickets), *SLC34A1* (AD hypophosphatemia with osteoporosis and nephrolithiasis; AR Fanconi syndrome), *SLC34A3* (AR/AD hereditary hypophosphatemic rickets with hypercalciuria) as well as *VDR* (AR vitamin D resistant rickets type 2A). Next-generation sequencing panels are now available for patients suspected of having heritable hypophosphatemia, although they may not yet be accessible in many countries. In some patients, DNA testing may be negative or may identify a variant of uncertain significance (VUS)—in these cases, the diagnosis of XLH relies 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, consideration can be given to re-interpretation of the variant classification in the future or assessment through a laboratory or specialist in variant interpretation.

Tumor-induced osteomalacia also results in FGF23-mediated renal phosphate wasting and should be considered in the differential diagnosis. It is caused by mesenchymal tumors which secrete FGF23 (31). Fanconi syndrome should be excluded by testing for aminoaciduria, glycosuria, normal anion gap metabolic acidosis, and low molecular weight proteinuria (10, 32, 33).

Role of bone histomorphometry. XLH is characterized by osteomalacia and peri-osteocytic "halo" lesions; the latter may be useful in distinguishing XLH from tumor-induced osteomalacia (34). Peri-osteocytic lesions also suggest a possible XLH diagnosis in patients with an "XLH-like phenotype" but without a detectable *PHEX* pathogenic variant. Trans-iliac histomorphometry is useful in demonstrating the bone tissue effect of medical therapy (with either burosumab or phosphate and active vitamin D) (35).

Role of bone mineral density assessment. A dual-energy x-ray absorptiometry (DXA) study is widely used to assess areal bone mineral density (aBMD); however, its application in all patients with XLH requires careful interpretation and further evaluation (36). In adult patients with XLH, aBMD often appears falsely elevated at the lumbar spine and tends to be decreased at the hip and 1/3 radial site (37). The lumbar spine aBMD may be falsely elevated due to ligamentous ossification, enthesopathies, and lamina thickening (23, 38, 39). In addition, the increased cross-sectional bone area leads to an overestimation of the aBMD in both children and adults (23, 38, 39).

Despite these limitations, DXA may with cautious interpretation, still have clinical utility in fracture risk assessment, and it can also be of benefit in postmenopausal women and men over 50 who may have superimposed osteoporosis in association with aging and hypogonadism (37, 39).

WHO TO TREAT?

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

Adults entering the XLH International Registry (NCT0319 3476) report high rates of skeletal symptoms/manifestations (71.8%) and problems with dentition (75.9% abscesses) (40). Some of these complications may respond to treatment and

Work up for Hypophosphatemia	
1	Inadequate intake or absorption: • Malabsorption – small bowel (celiac, Crohn's) • Vitamin D deficiency • Gut phosphate binders • TmP/GFR high or normal
2	Short term changes in serum phosphorus due to extracellular to intracellular shifts– influenced by insulin, glucose, catecholamines, rapid cell breakdown or growth or repair: • DKA treatment (insulin drives phosphate intracellular) • Refeeding syndrome • Hungry bone syndrome post parathyroidectomy • Acute respiratory alkalosis • Leukemia or lymphoma
3	Renal phosphate wasting – TmP/GFR LOW

Abbreviations: DKA: diabetes ketoacidosis; FGF23: Fibroblast Growth Factor 23; TmP/GFR: TmP/GFR: Tubular maximum phosphate reabsorption adjusted for glomerular filtration rate

Causes for Renal Phosphate wasting - TmP/GFR LOW

FGF23 HIGH	FGF23 LOW
Loss of function *PHEX* gene: X-linked Hypophosphatemia (XLH)	**Hereditary Hypophosphatemic Rickets with Hypercalciuria**: Loss of function in Na-P Type 2c gene; leads to phosphaturia and hypercalciuria
***FGF23* gene variants (ADHR)**: leading to mutant FGF23, resistant to cleavage; low iron (Fe) increases FGF23	**Fanconi Syndrome**: Renal glycosuria, amino acid losses, renal tubular acidosis, urine phosphate losses
***DMP1, ENPP1, FAM20C* gene variants (ARHR):** increase FGF23 expression	**Post Renal Transplant**: Occurs in approximately 50% of cases
***GNAS* gene variants (Fibrous Dysplasia/McCune-Albright Syndrome):** can lead to high FGF23 levels	**Drugs**: Aminoglycosides, cisplatin, tenofovir
Tumor-Induced Osteomalacia: FGF23 excess produced by mesenchymal tumors	**Heavy Metal Poisoning**: Lead
IV iron (especially ferrous carboxymaltose)	**Paraproteinemia**: Impairs renal tubular function
	Hyperparathyroidism: Decreased phosphate reabsorption

Figure 3. Workup for hypophosphatemia.

therefore, many experts recommend re-initiating medical therapy (with burosumab if available, or with conventional therapy if well tolerated) when clinical symptoms of osteomalacia, such as bone pain, osteomalacia-related fractures are present, during fracture healing of fractures or in preparation of skeletal/dental surgeries. In the adult population, the type and extent of previous treatment received will have an impact on the presence of current skeletal deformities as well as renal, parathyroid, and dental complications.

Treatment goals in adults are to normalize ALP, heal fractures, and improve bone pain and physical function. Normalization of fasting serum phosphorus is not in itself a treatment goal with conventional therapy. Treating with conventional therapy during adulthood may decrease but not eliminate dental abscesses or osteomalacia-related fractures. To date treatment in adulthood with conventional therapy or burosumab has not been shown to prevent or reverse the progression of enthesopathy or osteoarthritis. Conventional therapy in adulthood does not appear to be associated with excess cardiovascular risk (40, 41) but may be associated with chronic kidney disease (CKD), often in the presence of tertiary hyperparathyroidism (42). Only limited data are available regarding the effect of burosumab therapy on short-term patient outcomes in symptomatic adults (43).

Musculoskeletal Manifestations

Osteomalacia may result in bone and muscle pain as well as pseudofractures. Fractures and early osteoarthritis are also commonly observed (12, 44-47). An analysis study of clinical trial and survey data (n = 336) has shown that approximately 43% to 47% of adults with XLH had a history of fracture, with the proportions increasing with age (48). Joint damage occurs early and can be seen as early as the third decade. Bone pain, muscle pain, and muscle stiffness also contribute to decreased mobility. Enthesopathies initially manifest as calcification at the insertion sites of tendons and ligaments, eventually progressing to osteophyte formation (49, 50). Enthesopathies often develop bilaterally, involving weight-bearing joints and the spine and result in significant pain and impaired mobility. Currently, medical therapy has not been shown to prevent or effectively treat enthesopathies (51). Healing of pseudofractures and improvement in histomorphometric indices occur with burosumab therapy compared to placebo (4, 52). Musculoskeletal pain, stiffness, and mobility particularly respond to therapy (4, 52, 53).

Renal Complications

Renal complications in XLH include nephrocalcinosis (54), urinary stone disease (54), CKD (55), and hypertension (55, 56). Prevalence of nephrocalcinosis varies from 21% to 42% (47, 57) and up to 100% in some series (58). Severe nephrocalcinosis may lead to end-stage renal disease (59). Hypercalcemia and aggressive overtreatment, with development of hyperphosphatemia or elevations in the calcium × phosphate product, may also contribute to CKD.

More severe disease, as ascertained by height Z-score, correlates with a higher incidence of nephrocalcinosis (54). The incidence and prevalence of urinary stone disease in these patients is not well described. The prevalence of hypertension correlates with lower estimated glomerular filtration rate (eGFR) and the presence of CKD (55). Excess sodium intake may also occur with the use of oral sodium phosphate salts and may also contribute to the development of hypertension (55, 59, 60). Multiple other factors may also contribute to hypertension in addition to CKD and include decreased physical activity, obesity, and possibly elevated FGF23 (56). Additional disease-specific factors, such as *PHEX* gene–associated downregulation of the sodium phosphate cotransporter 2 (NPT2) (61), require further evaluation.

Thus, it is essential to monitor for nephrocalcinosis and hypercalciuria (16); reductions in the dose of active vitamin D may reduce the hypercalciuria, which can be further treated with

Table 1. Clinical features of adult XLH

Lower limb deformity
Fractures and pseudofractures
Muscle weakness and fatigue
Bone and joint pain
Dental infections and periodontal disease
Early joint damage
Enthesopathies
Spinal stenosis
Tinnitus, hearing loss
Osteophytes

hydrochlorothiazide (62) and/or potassium citrate (63). The eGFR should be monitored using the average (64) of the modified Schwartz formula (65) and the Filler formula (66) for cystatin C in patients aged 1.5 to 25 years of age (67-69) and the CKD-EPI formula for older patients, using both creatinine and cystatin C (70). CKD should be treated as per regional guidelines. This includes the use of angiotensin-converting enzyme inhibitors or angiotensin-2 receptor blockers (71, 72).

Hypertension should be treated as per current guidelines using the latest country- or region-specific guidelines for pediatrics and adults, if available (71-74) recognizing the differences among the American and European guidelines (75). Burosumab therapy may lower the blood pressure (56).

Neurologic Manifestations

Neurological complications of XLH in adults include headaches, craniosynostosis, Chiari 1 malformation, syringomyelia, spinal stenosis, spinal cord compression, tinnitus, and hearing loss. In an ongoing, multinational, prospective, longitudinal study designed to characterize disease burden, progression and long-term outcomes in XLH (the X-linked Hypophosphatemia Disease Monitoring Program [XLH-DMP]), neurologic complications were reported in 364 affected adults (76). Craniosynostosis was reported in 33/364 (9%), Chiari type 1 malformation in 19/364 (5.2%), syringomyelia in 6/364 (1.6%), and severe headache in 72/364 (19.8%). Neurological manifestations that are found more frequently in adults than in children with XLH are spinal stenosis, seen in 67/364 (18.4%), and spinal cord compression, seen in 37/364 (10.2%). Spinal stenosis and spinal cord compression in XLH may result from ossification of the ligamentum flava, thickening of the laminae, hypertrophy of facet joints, and intervertebral disc calcification. The XLH-DMP reports common occurrences of tinnitus (126/364; 34.6%) and hearing loss (106/364; 29.1%) in adults with XLH. Thus, comprehensive neurological and fundoscopic examinations should be performed in the presence of headache or other neurologic symptoms.

Hearing

Hearing loss, most often asymmetric, affects up to 34% of affected adults (57). Both sensorineural and conductive hearing defects may arise. Underlying mechanisms appear to involve both endolymphatic hydrops as well as osteosclerosis and thickening of the petrous bone (77). There is insufficient data at this time to assess the impact of treatment on the prevention and progression of hearing impairment.

Table 2. Disorders with hypophosphatemia

Disease	OMIM number	Gene(s) involved
FGF23-dependent		
XLH (X-linked hypophosphatemia)	OMIM#307800	*PHEX*
ADHR (autosomal-dominant fypophosphatemic rickets)	OMIM#193100	FGF23 *SKG3* (uncertain FGF23 status)
Autosomal-recessive hypophosphatemic rickets	OMIM#241520, #613312, 259775	*DMP1, ENPP1, FAM20C*
Hypophosphatemic rickets and hyperparathyroidism	OMIM#612089	*KLOTHO*
Osteoglophonic dysplasia	OMIM#166250	*FGFR1*
Opsismodysplasia (17)	OMIM#258480	*INPPL1*
Cutaneous skeletal hypophosphatemia syndrome (RAS)	OMIM#163200	*RAS*
Fibrous Dysplasia	OMIM#174800	*GNAS*
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 (18)	OMIM#241530	*SLC34A3*
Hypophosphatemia and nephrocalcinosis (19)	OMIM#182309	*SLC34A1*
X–linked recessive hypophosphatemic rickets: Dent disease (20)	OMIM#300009	*CLCN5*
Nephropathic cystinosis (21)	OMIM#219800	*CTNS*
Hypophosphatemia, nephrolithiasis, osteoporosis (22)	OMIM#604990	*NHERF1*

Quality of Life

The burden of disease is significant in both children and adults with XLH, with the majority experiencing some degree of pain, joint stiffness, fatigue, and impaired mobility and physical function that interfere with daily life (47, 78-81) and increase with age (80). Health-related quality of life (HRQoL) is reduced in adults with XLH compared to the general population (2, 47, 81, 82), with the physical component being the most consistently affected (47, 79, 81, 82) although some studies also report lower mental health scores (81-83). In adults, conventional therapy was shown to improve bone or joint pain in a small uncontrolled study (84) and was associated with better mental health scores in a cross-sectional study (2). Burosumab reduced pain, improved stiffness, fatigue, and physical function, and improved walking distance; however, only the improvement in stiffness was significantly favorable compared to placebo at 24 weeks in the pivotal adult RCT (4). These improvements persisted at 48 and 96 weeks in the open-label extension of this study (43, 52). Small short-term uncontrolled studies also

have shown that burosumab improves muscle performance, fatigue, and pain (85) as well as stiffness, physical function, and the physical component of HRQoL (86).

Currently there is insufficient evidence to support a recommendation on the impact of conventional therapy (phosphate and active vitamin D) on QoL.

Metabolic Dysfunction

Obesity and metabolic dysfunction have been reported in some patients with hypophosphatemic rickets. In the XLH21 study, a total of 21 patients with XLH (53%) had insulin resistance (HOMA > 2.4, N = 10 conventional therapy, N = 11 burosumab) (56). Another cohort study involving 113 patients with XLH reported that 56% of patients were overweight or obese (87).

Monitoring recommendations: follow-UP (GRADEd) (Fig. 4)

The following assessments in adults are advised **at least once a year unless otherwise specified:**
We suggest *(weak recommendations, very low certainty evidence)**

1. Pain assessment
2. Clinical assessment of fractures or pseudofractures by obtaining fracture history as well as physical examination for tenderness of regions with reported bone pain
3. Weight, standing height, and BMI measurement
4. Blood pressure measurement
5. Documentation of dental infections (abscesses or periodontitis)by history
6. Measurements of serum morning (fasting) phosphorus, total corrected or ionized calcium, ALP, creatinine or eGFR, PTH, 25-hydroxyvitamin D, spot urine phosphorus/creatinine ratio, spot urine calcium/creatinine ratio

Every 6 to 12 months:

7. Dental assessment
8. Clinical physical examination for skeletal deformity, osteoarthritis, and joint restriction

In the presence of neurological deficit:

9. Comprehensive neurological clinical examination

Annually or less frequent:

10. Renal imaging, preferably with renal ultrasound

Annually in the presence of bone pain:

11. Skeletal survey or x-rays to screen for fractures or pseudofractures

Practices that we suggest are not routinely required (discretionary):

12. Routine sitting height measurements
13. Routine QoL assessment

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

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; QoL, quality of life.

HOW TO TREAT?

Treatment recommendations* (GRADEd) (Fig. 5)

1. In adults with fractures or pseudofractures ***we recommend*** burosumab therapy over no therapy (*strong recommendation, moderate certainty*).
2. In adults without fractures or pseudofractures ***we suggest*** burosumab therapy over no therapy (*conditional recommendation, low certainty*).
3. In adults with fractures or pseudofractures ***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. Provide ongoing care by an expert in metabolic bone disease who recognizes the importance of multidisciplinary services at the transition to adulthood—along with patient support groups—to address disease-related comorbidities.
2. Continue medical therapy (with either burosumab or phosphate and active vitamin D) for at least several years following epiphyseal closure enabling the optimization of peak bone mass which occurs at approximately 20 to 25 years of age in asymptomatic individuals.
3. Provide medical therapy (with either burosumab or phosphate and active vitamin D) in the presence of symptoms or biochemical/histological evidence of osteomalacia (bone pain, weakness, osteomalacic fractures, elevated ALP, or osteomalacia on bone biopsy)
4. Optimize medical therapy (with either burosumab or phosphate and active vitamin D) prior to undertaking orthopedic surgeries or dental implant surgeries.
5. Provide ongoing adult care with pharmacotherapeutic management (with either burosumab or conventional therapy) with consideration of the benefits and risks of therapy and the patient's capacity for ongoing monitoring.
6. 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.
7. If burosumab is not available, symptomatic adults should be treated with conventional therapy (active vitamin D with or without phosphate salts).
8. Phosphate salts should not be used as monotherapy.
9. When treating with conventional therapy (active vitamin D with or without phosphate salts), the fasting serum phosphorus should not serve as a target. It is not necessary to achieve normal fasting serum phosphorus levels

to treat XLH, and the high phosphate loads used to accomplish this often lead to severe hyperparathyroidism.
10. Treatment with active vitamin D and phosphate salts should be modified to avoid hypercalcemia and hypercalciuria.
11. Burosumab is contraindicated in CKD (GFR less than 30 mL/min), and in acute kidney injury. Cautious use may be considered in the presence of an eGFR between 30 and 60 mL/min with careful monitoring.
12. Treat hypertension using current regional recommendations pertaining to hypertension management.
13. Treat tertiary hyperparathyroidism in the setting of hypercalcemia, where multi-gland involvement is anticipated, with off-label use of calcimimetics (ie, cinacalcet) to lower PTH levels, with careful monitoring of serum calcium to prevent hypocalcemia. If hyperparathyroidism and hypercalcemia remain uncontrolled, a subtotal parathyroidectomy should be considered.
14. Treat hypercalciuria by reducing the dose of active vitamin D, and in persistent hypercalciuria, hydrochlorothiazide or potassium citrate may be used. The panel also proposes a low sodium intake (<1500 mg/day) and increased fluid intake up to 3 L/24 hours in the presence of hypercalciuria.
15. Early referral to the spinal team with physiotherapy in cases of spinal scoliosis.
16. Treat spinal scoliosis with surgical fixation if the Cobb angle is greater than 30 degrees depending on the rate of progression and location of the curve.

Conventional Therapy

Generally, symptomatic adults with XLH are treated with phosphate salts (750-2000 mg/day) divided into 3 to 4 doses daily, and active vitamin D (calcitriol [0.5 to 1 μg/day] or alfacalcidol [0.75-1.5 μg daily]), especially when treating osteomalacia or fractures. Doses may then be lowered during the maintenance phase of treatment to minimize long-term complications (11, 24, 49). A balanced use of calcitriol (useful in dampening PTH secretion) and phosphate is of value in order to avoid phosphate stimulation of PTH, which exacerbates renal phosphate loss and further lowers serum phosphate. Importantly, phosphate salts should not be used as monotherapy without concurrent active vitamin D. Active vitamin D without phosphate salts, however, may be considered in adults with mild symptoms.

Adequate dietary calcium intake is recommended to provide calcium for skeletal mineralization and the healing of osteomalacia and rickets, especially during the first few months of treatment, acknowledging that the active vitamin D also increases gastrointestinal calcium and phosphate absorption, and the combination may increase the risk of hypercalciuria. As calcium supplements act as phosphate binders, potentially reducing the bioavailability of phosphate supplements, calcium intake must be separated 1 hour from phosphate intake. Elevated PTH with concomitant low urinary Ca/Cr may indicate the need for increasing the calcium intake.

Phosphate supplementation is often limited by gastrointestinal tolerability issues, including dyspepsia, and a laxative effect. Patients may opt to discontinue phosphate replacement due to gastrointestinal side effects. As mentioned above, complications of conventional therapy include secondary and tertiary (hypercalcemic) hyperparathyroidism, nephrocalcinosis, and CKD. Tertiary hyperparathyroidism occurs in about 25% to 30% of adults with XLH (88) and may develop several years after stopping conventional therapy. The resulting hypercalcemia limits the use of active vitamin D. Tertiary hyperparathyroidism usually requires multi-gland parathyroidectomy, and hypercalcemia can still recur. Cinacalcet may be effective as adjunctive therapy for hyperparathyroidism (89-91).

Burosumab

In adults, burosumab is administered at a starting dosing of 1 mg/kg every 4 weeks, with an approved maximum of 90 mg every 4 weeks, based on the dose used in the placebo-controlled trial in adults (4). This trial indicated that burosumab normalized serum phosphorus and the healing of active osteomalacia-related fractures (52). In the RCT comparing burosumab to placebo, burosumab positively impacted various QoL measures as noted above (4, 52, 92-94). However, when applying GRADE to assess the certainty of evidence with respect to QoL measures, burosumab showed little or no impact on fatigue or mobility. Burosumab also demonstrated probably little or no impact on pain and stiffness when using direct measures of pain and function. Dental abscesses appeared to be more with burosumab compared to placebo in the trial over 24 weeks (5% more; 95% CI, −5 to 16) (95).

Joint damage and enthesopathy are among the most debilitating symptoms of XLH in adults, beginning even in the third decade of life. Unfortunately, there is no evidence to date that either conventional therapy or burosumab in adults prevents joint damage or enthesopathy and further research is required.

Monitoring of burosumab requires frequent laboratory testing for both safety and efficacy as with conventional therapy. In contrast to conventional therapy, the target with burosumab is to achieve a normal fasting serum phosphorus concentration throughout the dose cycle, if possible, while avoiding hyperphosphatemia. Thus, the interpretation of every laboratory assessment requires consideration of its relationship in time to the last dose of burosumab. In clinical trials, the peak serum phosphorus value was observed at 7 days post-dose (53), while TmP/GFR peaked 7 to 14 days post-dose. Serum $1,25(OH)_2D$ peaks at day 3 to 7 after burosumab dose and the mean value is supraphysiologic. Hypercalciuria or hypercalcemia may theoretically occur early in the dosing cycle when or shortly after $1,25(OH)_2D$ levels peak, especially in patients with parathyroid autonomy or high calcium intake.

Achieving a normal fasting serum phosphorus throughout the dose cycle with burosumab is challenging and not all adults achieve normal fasting serum phosphorus with doses of up to 90 mg of burosumab every 4 weeks. In order to achieve consistently normal fasting serum phosphorus with burosumab therapy, some patients may require more frequent dosing than every 4 weeks and may require dosing every 2 weeks. The total monthly dose may be more than 90 mg in a 4-week period. These are currently off-label regimens. In contrast, some patients may require very low burosumab doses in order to normalize fasting serum phosphorus, highlighting the broad individual variation in response.

Complications of hyperparathyroidism in adults may be less likely to occur with burosumab. In a recent clinical trial reductions in PTH levels were noted with burosumab in comparison to placebo (52). Injection site reactions occur in adults

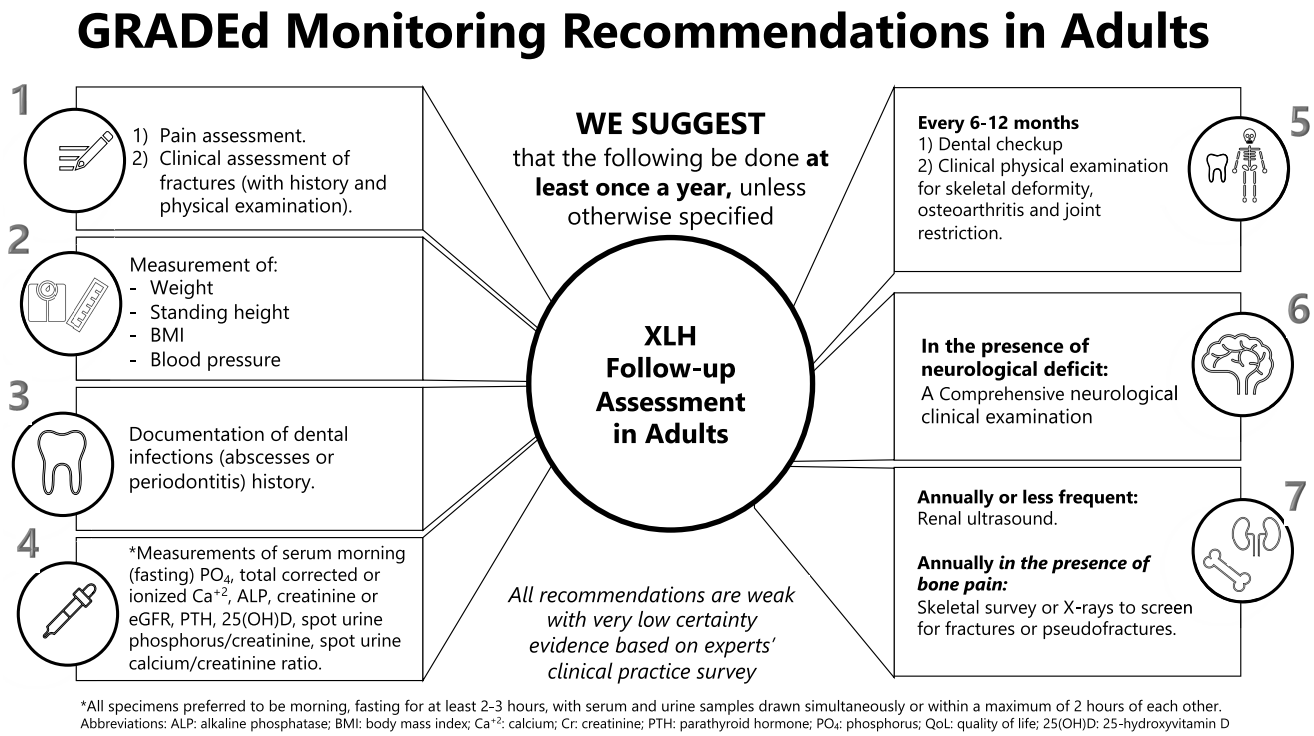


Figure 4. GRADEd monitoring recommendations for follow-up in adults with XLH.

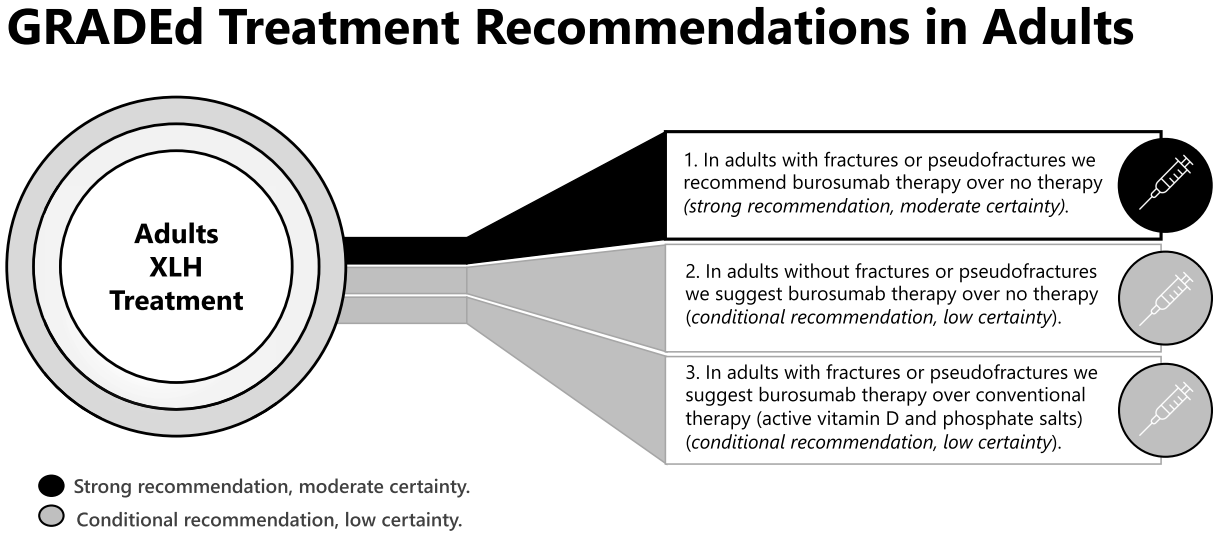


Figure 5. GRADEd treatment recommendations in adult XLH.

less commonly than in children and are typically brief and usually do not require discontinuation. Occasionally patients have reported transient generalized bone pain at the onset of therapy. About 8% (or more) of patients with XLH have restless legs syndrome in the absence of burosumab therapy. Restless leg syndrome has been noted as an adverse event of burosumab therapy (4).

Orthopedic and Related Surgical Procedures

Orthopedic intervention for XLH is predominately devoted to fracture care and osteotomies performed to correct limb alignment. Fractures and deformity occur primarily in the lower extremities and are attributed to progressive osteomalacia and the impact of prolonged weight bearing on poorly mineralized bones and misaligned joints. Reports of surgical treatment of bone deformity in skeletally mature adults with XLH include small numbers of patients with no control groups. The few articles specific to surgical treatment in adults with XLH promote intramedullary fixation (rods) for realignment osteotomies to span the full length of the bone; this approach allows for long healing time and prevents recurrence of deformity over the long term. In general, however, surgical management should be coordinated between the surgical team and the metabolic bone disease specialists. For most skeletal surgeries, surgical healing of the bone is likely to be

improved with antecedent medical therapy (with either burosumab or phosphate and active vitamin D). Improved healing of active fractures after starting burosumab therapy was noted in the RCT study evaluating burosumab in comparison to placebo (before which many participants were receiving conventional therapy), supporting the use of burosumab for postoperative skeletal healing (4).

Pseudofractures

Pseudofractures are areas of weakened bone that appear as transverse radiolucent lines on imaging studies, varying in width from less than a millimeter to over a centimeter (96). They often indicate underlying skeletal weakness or dysfunction due to metabolic bone diseases such as osteomalacia. These lesions have been referred to as Looser's zones (97), insufficiency fractures (98), and osteomalacia-related fractures. The aims of therapy are to heal fractures and to prevent complications. If a pseudofracture is at high risk of progressing to a full-thickness fracture or worsening deformity, initiating burosumab therapy is advised. If burosumab is not available, conventional therapy should be considered, despite insufficient data on its impact on fracture healing. Strong evidence supporting the use of burosumab to enhance fracture or pseudofracture healing is available (4). Consider referral for surgery if there is evidence of deformity or severe pain that is not responding to medical therapy (with either burosumab or phosphate and active vitamin D). Complete fractures or pseudofractures may still require prolonged healing time, even with conventional therapy or burosumab, as noted in the RCT in which only 63% of the active fractures at baseline were completely healed at 48 weeks of therapy (52).

Complete fragility fracture

The goal of treatment is to fix the fracture, optimize the anatomy and function and promote recovery. The bone is likely to be soft in the presence of a mineralization defect, and therefore nailing may be preferable to plating. A specialized orthopedic team should be consulted in the presence of significant deformity that may be multi-planar. In the RCT improved radiographic healing of active fractures and pseudofractures was observed in the burosumab arm in comparison to placebo in adults over 24 weeks (4). In our accompanying systematic review, there was a 35% improvement in fracture and pseudofracture healing with a narrow CI (95% CI, 22 more to 49 more) with burosumab in comparison to placebo (95).

Other Elective Orthopedic Surgeries, Including Arthroplasty

If musculoskeletal pain is present, further evaluation is required to determine the cause. Advanced joint disease may require arthroplasty. A recent survey of musculoskeletal complaints in adults with XLH emphasized both the high frequency and early onset of musculoskeletal conditions, including osteoarthritis requiring hip and knee arthroplasty in adults as young as 30 years of age.

Scoliosis and spinal stenosis

Patients with scoliosis should be regularly monitored for progression as assessed by pain or worsening deformity.

Spinal stenosis is a complication of XLH and may require surgical intervention (48). Patients with XLH should be monitored for symptoms of neurologic compromise and undergo spinal imaging in the presence of nerve or spinal cord compression with referral to surgical specialists. Patients may require laminectomy and spinal fusion procedures.

Patient Support Groups

Patient support groups play a crucial role in the care of adults with XLH. Organizations such as the XLH-Network (https://xlhnetwork.org/) and the Canadian XLH-Network (https://canadianxlhnetwork.org/), among others, provide valuable resources, education, community, and peer to peer support for patients of all ages. They offer information on disease management, transition from pediatric to adult care, and self-care strategies. They also provide valuable information regarding how and where to access specialized multidisciplinary team care. Support groups are of great value in assisting patients with XLH in navigating the healthcare system. Psychological support is also an unmet need and patient support groups may be of value in locating community resources (99, 100). By providing a platform for shared experiences and advocacy, patient support groups empower adults with XLH to take an active role in their healthcare and may contribute to improve their QoL.

PREGNANCY AND LACTATION

Preconception and pregnancy (GRADEd)

For follow-up assessment during preconception and pregnancy:

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

1. Providing genetic counseling to all women of childbearing age, including adolescents, regarding the inheritance of XLH and the risk of transmission
2. Counseling women of childbearing age (including adolescents) who are treated with burosumab or conventional therapy (phosphate salts and active vitamin D) regarding the limited evidence of the risks and benefits associated with these treatments

In the presence of neurological deficit:

3. Conduct a comprehensive neurological clinical examination for patients presenting with neurological deficits

Biochemistry:

4. Measurement of serum total calcium (albumin corrected) or ionized once every trimester for all women; serum creatinine and eGFR measurement monthly for women on medical therapy; and fasting serum phosphorus at least once during pregnancy for all women.

Practices that we suggest are not routinely required during pregnancy (discretionary):

5. Mobility assessment with 6MWT during pregnancy
6. QoL assessment
7. Renal ultrasound to screen for nephrocalcinosis during pregnancy

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

Abbreviations: 6MWT, 6-minute walking test; eGFR, estimated glomerular filtration rate; QoL, quality of life.

RECOMMENDATIONS FOR PREGNANCY AND LACTATION (NON-GRADEd)

The Panel Proposes

1. Optimization/normalization of serum corrected calcium, and vitamin D levels preconception, during pregnancy, and while breastfeeding. This may involve considering surgical intervention pre-conception in cases of existing tertiary hyperparathyroidism (the ideal target for fasting serum phosphorus in pregnancy is not known at this time).
2. Medication review should be performed preconception:
   (a) Thiazide diuretics, angiotensin-converting enzyme inhibitors or angiotensin-2 receptor blockers, should be stopped.
   (b) Cinacalcet is not recommended during pregnancy (FDA category C). Data regarding the safety of cinacalcet in pregnancy is limited. It has been successfully used in nonpregnant individuals with XLH and hyperparathyroidism.
   (c) Safety of burosumab treatment during pregnancy and lactation is not established. Risks and benefits of therapy should be discussed with patients. There is inadequate data at this time to make a recommendation regarding burosumab therapy during pregnancy.
3. Phosphate supplementation is ideally divided into 4 to 5 daily doses, and always in combination with active vitamin D, (calcitriol is given twice daily given the short half-life and alfacalcidol is given once daily).
4. Lower doses of phosphate and active vitamin D may be sufficient in pregnancy due to increased endogenous production of $1,25(OH)_2D$. However, close monitoring is required, as requirements for conventional therapy may vary among patients.
5. Blood pressure monitoring at every pregnancy visit; and treatment for hypertension should be initiated in collaboration with the obstetrician, both preconception and during pregnancy. This should follow the current regional recommendations pertaining to hypertension management.
6. Close monitoring of serum corrected calcium during lactation with modifications of active vitamin D in cases with existing secondary/tertiary hyperparathyroidism, as hypercalcemia may worsen due to rises in parathyroid hormone-related protein (PTHrP).
7. Normalization of bone-specific alkaline phosphatase (BsALP) by ensuring adequate calcium intake, active vitamin D, and native vitamin D supplementation during pregnancy.
8. Monitoring breastfed infants of affected mothers to ensure their serum phosphorus levels are normal.

Preconception Planning. Women of childbearing age with XLH should receive preconception advice and multidisciplinary counseling regarding the inheritance pattern, and possible complications of pregnancy or drug therapy in XLH. The involvement of a genetic counselor is useful. Prenatal and preimplantation genetic testing for XLH may be considered as possible options in some contexts (101). In addition, the utilization of embryo selection may also be discussed if available and amenable.

Pregnancy and Lactation

Physiological changes. Pregnancy results in changes in calcium and phosphorus homeostasis. These changes are beneficial in supporting fetal skeletal development and growth and include elevations in parathyroid-related protein (PTHrP) and $1,25(OH)_2D$ as noted in pregnant women with normal phosphate homeostasis (102). Some data suggest that TmP/GFR is not affected by pregnancy (103), while others report rises in TmP/GFR in the first trimester (104). Intact FGF23 levels seem unaffected by pregnancy in healthy individuals, but this has not been studied in women with XLH (105). In the case of XLH, these physiological alterations may impact serum phosphorus and potentially increase pregnancy complications.

Management of maternal XLH during pregnancy and lactation. There is limited evidence to support specific guidance on the management of XLH during pregnancy and lactation. Most data are derived from case reports and case series. During pregnancy, production of $1,25(OH)_2D$ from the placenta and breast increases serum calcium levels and urinary calcium excretion, warranting close monitoring (106).

Frequent laboratory testing during pregnancy (every 1-2 months) is prudent for safety monitoring. The safety of burosumab treatment during pregnancy and lactation is not established. The risks and benefits of therapy should be discussed with patients. There are inadequate data at this time to make a recommendation regarding burosumab therapy during pregnancy.

The data on mode of delivery in XLH are heterogeneous. In a report of 22 deliveries in 12 women with XLH, only 7 vaginal deliveries (32%) were reported, while the remaining required cesarean delivery (46). Similarly, a cohort study from the UK reported a higher rate of cesarean deliveries in 18 women with XLH, with 8 of 34 deliveries (23.5%) via the vaginal route (57). In contrast, a Danish study of the 60-year period from 1946 to 2006 found that only 3 of 25 women with XLH (in 5 of 36 pregnancies; 14%) underwent a cesarean delivery, not significantly different from the general population (23).

Management of maternal XLH to improve fetal outcomes. To date, there is no evidence for any benefit to the affected fetus from treatment of maternal XLH. In the *Hyp* mouse model of XLH, the affected pups were normophosphatemic in utero despite the hypophosphatemia in the affected dam (107). It appears that FGF23 is not required to regulate fetal phosphate metabolism. Physiologic disturbances begin to affect phosphate metabolism only after birth (108). Of note, burosumab does cross the placenta, and effects on the developing fetus are not known. Close monitoring of the clinical and biochemical status of women with XLH throughout pregnancy is advised during treatment with conventional therapy, given the known effects of pregnancy on mineral homeostasis. Some clinicians reduce dosing of conventional agents during this time (109).

DENTAL and ORAL COMPLICATIONS

DENTAL RECOMMENDATIONS (NON-GRADEd)

The Panel Proposes

1. Dental visits at least once a year to screen for infections, and periodontal supportive care with recall intervals based on each individual condition.
2. In the presence of active oral manifestations, treatment with active vitamin D and phosphate salts, or burosumab

is advised to reduce the risk of dental infections and the severity of periodontitis.

RECOMMENDATIONS FOR DENTAL PROFESSIONALS (NON-GRADEd)

The Panel Proposes

1. A thorough clinical and radiological assessment searching for spontaneous pulp infection (tooth color changes, fistula, swelling, abscess, cellulitis, pain, periapical bone loss), and periodontitis.
2. Performing a dental orthopantomogram (radiograph of the upper and lower jaw and teeth), potentially complimented or replaced with cone-beam computed tomography imaging, in patients with recent oral manifestations, which can be repeated based on individual needs.
3. Implant surgery may be performed after 3 to 6 months of medical treatment (conventional therapy or burosumab), which should be continued for 6 months following implant surgery; healing time should be extended up to 6 months.

Dental complications are common in patients with XLH (3, 49, 110) and significantly alter QoL (111-113). Mineralization of dentin is impaired, resulting in greater susceptibility to pulp infections (114, 115). Periodontal tissues are compromised (3, 116, 117) resulting in relatively frequent and severe periodontal diseases in affected adults of all ages (3, 118), premature loss of teeth (3, 110), as well as an increased risk of dental implant loss (47).

Prevention and Management of Dental Complications of XLH. Multidisciplinary teams caring for patients with XLH must include dental services (12, 24, 25). In adults, twice-yearly visits are indicated to perform conventional supportive periodontal therapy (24). Dental implant placement should not be performed in the absence of medical treatment. It is suggested that implant surgery be performed after 3 to 6 months of medical treatment (expert recommendation), with continuation for at least 6 months following the implant surgery (24, 119, 120). For all patients, bitewings and/or periapical radiographs, orthopantomogram or cone-beam computed tomography may be performed based on clinical needs (24, 121-123); malocclusions may be present (124). Medical therapy (with either burosumab or phosphate and active vitamin D) should be started prior to initiation of any required orthodontic treatment.

Comparison of the Effect of Therapies (Burosumab and Active Vitamin D/Phosphate Salts) on Dental Complications of XLH. Early conventional treatment with good compliance improves dentin and potentially cementum mineralization (3, 114), reduces dental infections in children and adults, and decreases the severity of periodontitis in adults (3, 49, 114, 125). Limited studies have compared the effects of burosumab with those of conventional therapy on dental manifestations of XLH in adults. In a recent RCT in adults, burosumab was not found to reduce the number of dental abscesses compared to placebo, However, dental outcomes were not included as a study endpoint measure in the study design and ascertainment was questionable (4). In this 24-week study, 9 of the 68 adult patients (13.2%) treated with burosumab developed an abscess compared to 5 of the 66 patients (7.6%) in the placebo arm. Further long-term data is being obtained.

RESEARCH AGENDA

Much remains to be explored in terms of understanding the full adult phenotype of XLH and optimizing therapy to minimize morbidity. For instance, it is not understood which features of XLH are mediated by hypophosphatemia and which are independent of hypophosphatemia. Exploration into the direct effects of *PHEX* loss of function and chronic exposure to ambient elevations in FGF23 is warranted. On a molecular level, understanding the function of *PHEX* with respect to its substrate, its interaction with FGF23, and its full physiologic effect remains elusive and an active area of investigation. It will be important to determine whether long-term inhibition of FGF23 activity can result in normalization of bone histomorphometric measures that were found to be partially but not completely corrected after 1 year of burosumab treatment (35). Other critical gaps in knowledge include understanding the etiologies of arthritis and enthesopathy, and their responsivity to inhibition of FGF23 activity, both acutely and with respect to long-term preventive approaches. Likewise, the therapeutic response of dental disease, hearing loss, craniosynostosis, and associated central nervous system complications remains unknown. The full burden of XLH is likely underestimated. QoL, loss of productivity, and the economic burden of the untreated XLH patient need to be estimated. On a more immediate scale, clinical experience to date would suggest optimization of treatment schedules with attention to dosing intervals is an important area to investigate, as worsening clinical symptomatology appears to recur near the end of the currently approved "every 28-day" dosing cycle. Thus, there is a broad opportunity to further improve the management of the adult patient with XLH.

Summary

These global XLH guidelines have been developed based on systematic reviews of the literature, GRADE methodology to evaluate the certainty of evidence, and broad consensus using surveys among international experts in XLH. The guidelines provide recommendations for the diagnosis and management of XLH in adults today. XLH is associated with significant multisystem complications, including musculoskeletal, dental, neurologic, renal, parathyroid, and ocular effects. A careful clinical assessment is required to confirm the correct diagnosis and to evaluate the multisystem manifestations, including the impact on daily function and QoL. A specialized multidisciplinary team is recommended to optimize care for various aspects of disease progression and to manage pharmacologic and potential surgical interventions. Conventional therapy with phosphate salts and active vitamin D is of value in improving bone mineralization and likely useful for enhancing healing of fractures, as well as preventing and treating dental complications. Complications of conventional therapy include secondary or tertiary (hypercalcemic) hyperparathyroidism, nephrocalcinosis, and impairment in renal function. Hyperparathyroidism may be less likely to occur with burosumab therapy.

Surgical intervention may be required in the presence of severe spinal stenosis, advanced scoliosis, or advanced joint disease. Medical therapy (with either burosumab or phosphate and active vitamin D) prior to surgical intervention is advised to optimize bone mineralization and surgical outcomes.

Close monitoring of any therapy during pregnancy and lactation is advised. Conventional therapy may be safe during pregnancy, although some clinicians decrease the dosing.

Burosumab has been demonstrated to improve active fracture and pseudofracture healing in comparison to placebo. In adults with fractures or pseudofractures burosumab is recommended over no therapy (strong recommendation). Burosumab is also suggested over conventional therapy in the presence of fractures or pseudofractures (conditional recommendation) based on the results of the SRs conducted. Appropriate revision of these clinical guidelines would be useful in several years with the development of a greater body of knowledge and clinical experience.

Limitations

Our recommendations are limited in assessing patients' functional status, as we primarily considered the 6-minute walking test (6MWT) for evaluating mobility. Our survey did not address other important aspects of function, such as walking perimeter, use of assistive devices, or daily activity levels. Moreover, the use of the 6MWT did not achieve the consensus threshold in our survey, reflecting variability in clinical practice.

Endorsement

To date, this manuscript has been endorsed by the following societies: The American Society for Bone and Mineral Research (ASBMR), the Argentinian society, the Brazilian Association of Bone Assessment and Osteometabolism, the Canadian XLH-Network (patient group), The Canadian Society of Endocrinology and Metabolism (CSEM), the Chilean Society of Osteology and Mineral Metabolism (SCHOMM), the Endocrine Society, the European Calcified Tissue Society (ECTS), the European Reference Network on Rare Bone Diseases (ERN BOND), the French Dental Association, the German Society of Endocrinology, the German Society of Osteology, the International Osteoporosis Foundation (IOF), the Irish Endocrine Society (IES), the Japanese Society for Bone and Mineral Research (JSBMR), the Kuwait Academy of Rare Diseases (KARD), Osteoporosis Canada, the Pediatric Endocrine Society (PES), and XLH Denmark (patient group).

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Author Contributions

Design/conceptualization of the Project: A.A.K., D.S.A., R.M., G.G. Data acquisition, review, analysis, methodology: A.A.K., D.S.A., H.A.A., F.A., S.H., R.M., G.G. Project Administration, including acquisition of funding: A.A.K. Original drafting and preparation of the manuscript: A.A.K., D.S.A., N.M.A., T.O.C., C.C., E.A.I., S.J.d.B., P.F., R.T.A., F.A., S.S.B.N., M.B.D., R.K.C., K.D., G.F., S.F., P.G., Co.G., M.K.J., A.K., E.M.L., C.M., A.M., H.S., S.T., L.T., L.M.W., G.G., M.L.B. Review/editing of the manuscript: A.A.K., D.S.A., N.M.A., T.O.C., C.C., E.A.I., S.J.d.B., P.F., H.A.A., R.A., R.T.A., F.A., S.S.B.N., M.B.D., M.C.S., R.K.C., K.D., G.F., L.F., S.F., C.G., P.G., Co.G., Ch.G., S.H., M.K.J., S.K., A.K., A.L., W.F.L., E.M.L., C.M., R.M., E.M., A.M., A.A.P., Y.R., E.T.R., H.S., S.T., L.T., L.M.W., G.G., M.L.B.

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Data Availability

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

Ethical Statement

The objective of this study is to evaluate the current evidence on the diagnosis and management of X-linked hypophosphatemia and did not require ethical committee approval.

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