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SPECIAL REPORT

Methodology for the international working group clinical practice guidelines on X-linked hypophosphatemia in children and adults

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Abstract

The guideline panel, comprising international experts in X-linked hypophosphatemia (XLH), patient partners from the XLH patient population, and guideline methodologists, held 18 teleconferences between January 2023 and July 2024 to develop comprehensive guidelines for the diagnosis and management of XLH in children and adults. For a subset of our questions, we utilized the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology, assessed the certainty of evidence and formulated GRADEd recommendations. For these questions, the panelists and methodologists collaboratively framed PICO (Population, Intervention, Control, and Outcomes) questions and conducted four systematic reviews assessing the impact of medical therapy—using either burosumab or phosphate and active vitamin D—on patient-important outcomes in the XLH population as well as the impact of medical intervention compared to no treatment. We assessed the risk of bias and transparently generated summary of findings tables using MAGICApp. The panel developed three GRADEd treatment recommendations for adults and two for children. Each GRADEd recommendation was linked to an underlying body of evidence, reflecting judgments on the certainty of evidence, recommendation strength, values, preferences, and considerations of costs, feasibility, acceptability, and equity. Due to the paucity of evidence, the panel developed very low-quality GRADEd recommendations on monitoring patients with XLH based on an expert clinical practice survey. Using a rigorous narrative literature review, the panel developed non-GRADEd recommendations including guidance for pregnant women, patients with dental complications, and other areas where evidence is limited. This article summarizes the methodology utilized for the development of both GRADEd and non-GRADEd recommendations for patients with XLH.

Background

In this paper, we describe the methodology for the guidelines on the diagnosis and management of X-linked hypophosphatemia (XLH) in children and adults. An international working group (IWG) of experts in XLH and methodology held 18 virtual meetings to develop these guidelines providing a comprehensive, evidence-based approach to the management of XLH. The guideline IWG along with the methodology team conducted four systematic reviews as well as narrative reviews to address:

1) Diagnosing XLH
2) Selecting patients with XLH for treatment
3) Treating patients with XLH
4) Monitoring patients with XLH
5) Managing XLH in pregnancy and lactation
6) Managing the dental complications of XLH
7) Research agenda

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For some recommendations, the methodology involved the use of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system to evaluate and grade recommendations for clinical practice based on the quality of evidence and strength of recommendation [1]. The panel also developed non-GRADEd statements for questions with insufficient evidence to conduct systematic reviews.

Composition, selection, and function of the guideline IWG

The chair (AAK) and co-chair (DSA) invited experts with clinical expertise in the management of XLH from various clinical backgrounds including clinical and research experience, reflecting geographic representation to participate in the guideline IWG. Equal preference was given to both men and women. The guideline IWG comprised 50 interdisciplinary members from Canada, the United States, South America, Europe, and Asia. This group included pediatric and adult endocrinologists, nephrologists, rheumatologists, orthopedic surgeons, dentists and oral surgeons, clinical geneticists, methodologists, and patient representative with XLH (27/50 females). The guideline IWG met virtually in 18 engagements over 18 months and worked closely with the methodology team to define the scope and approach to developing the guidelines (Fig. 1).

Guideline process

The team conducted four systematic reviews: two evaluated the impact of medical therapy with either burosumab or conventional therapy (phosphate salts and active vitamin D) on patient-important outcomes as well as the impact of medical intervention compared to no treatment in children, and two assessed the same impact in adults (see Fig. 2). For the section on "Diagnosing XLH", the IWG developed non-GRADEd recommendations informed by a narrative review of the literature. Due to the limited available evidence, the sections on "Selecting Patients with XLH for Treatment" and "Treating Patients with XLH" used a combination of systematic literature review (GRADEd recommendations) and a less structured process (non-GRADEd) to develop treatment recommendations. The section on "Monitoring patients with XLH" was informed by an expert clinical practice survey covering different aspects of XLH monitoring (GRADEd recommendations, very low-certainty evidence). This included assessment of new patients as well as characteristics requiring monitoring in children and adults including pregnant women. Monitoring recommendations were also developed for dental complications. Some of the recommendations related to pregnancy and dental assessment were non-GRADEd and were based on narrative reviews. The guideline development process was inclusive, with a

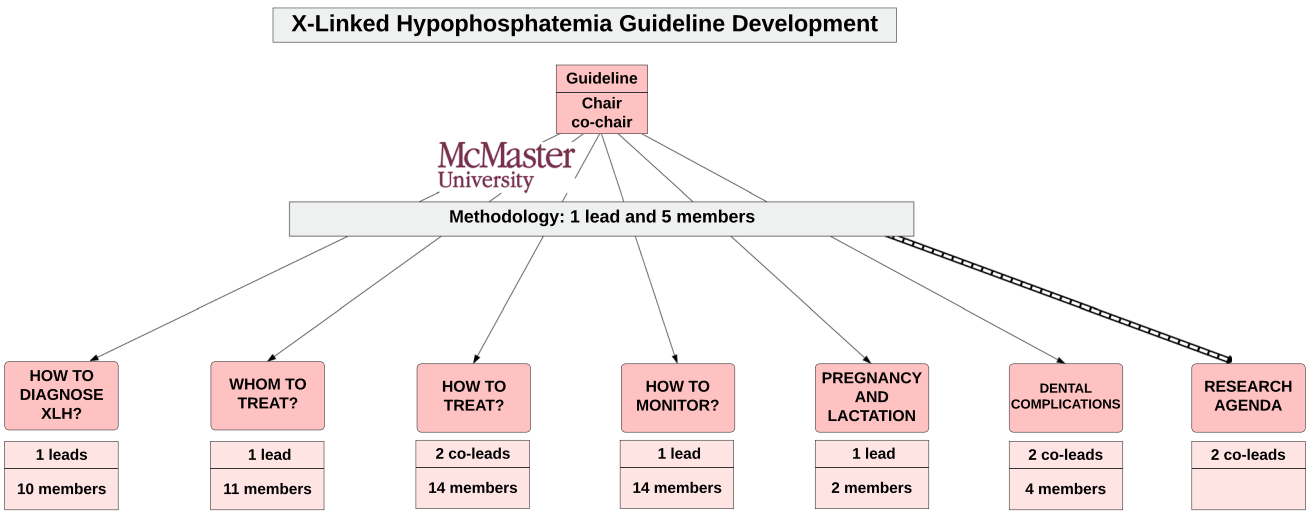

Fig. 1 Guideline committee composition. The chair of the IWG (AAK) assigned a lead from the team to coordinate the formulation of each section of the guideline (Figure 1) in collaboration with other team members. The lead (PF) led the section on 'Diagnosing XLH'. The chair (AAK) took the lead in the section on 'Selecting patients with XLH for treatment', while (MLB and EAI) co-led the section on 'Treating patinets with XLH'. The co-chair (DSA) led the section on 'Monitoring patients with XLH.' (NMA) led the narrative on 'Managing XLH in pregnancy and lactation,' and (CC with AM) led the narrative on 'Managing the dental complications of XLH.' Lastly, the co-leads (SJdB and TOC) led the section on 'Research agenda?. The chair also invited participation from methodologists from McMaster University, led by (GG), with expertise in guideline development and the co-chair of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.

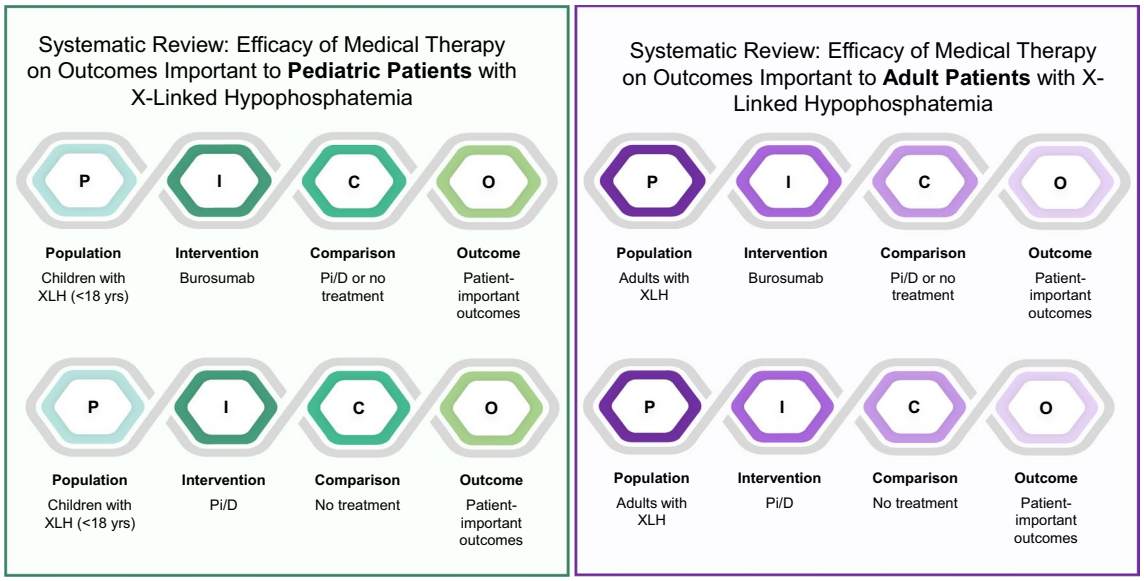

Fig. 2 Structure of the four systematic reviews that informed the guidelines treatment recommendations. *Pi/D* phosphate salts and active vitamin D analogues; *XLH* X-linked Hypophosphatemia

patient partner representing patient care societies involved in all aspects of the guideline formulation.

Recommendations of the guideline paper

GRADEd recommendations

Our GRADEd recommendations were developed following a structured approach using systematic reviews. This will be discussed in detail in this manuscript [2, 3].

Non-GRADEd recommendations

These recommendations were based on a narrative review of the literature and are clearly described as non-GRADEd in the guidelines.

All recommendations, GRADEd or non-GRADEd, were developed following a consensus reached amongst the IWG members over several meetings.

Structured questions for the GRADEd recommendations

Evidence review

GG led a team of methodologists and clinicians (DSA, RM, HAA, FA, and SH) who conducted four systematic reviews. The experts from the IWG provided support throughout the process. The team published the outcomes of these reviews as individual reports.

Defining the clinical questions

The IWG established the scope of the guidelines. They developed six questions using a comprehensive structural approach, beginning with defining the population of interest, followed by the intervention or exposure, the comparator, and patient-important outcomes (PICO format), as presented in Fig. 3. Over two virtual meetings, the IWG selected patient-important outcomes, dividing them into children-specific (< 18 years) and adult-specific (≥ 18 years) categories based on the population of interest. Additionally, the IWG expressed interest in evaluating several surrogate outcomes, as outlined in Fig. 3.

Literature search

The methodology team, with the assistance of a senior health sciences librarian (RC) experienced in systematic reviews, developed the search strategy for each of the PICO questions. The search was conducted from inception to May 2023 in four databases: MEDLINE, Web of Science, EMBASE, and Cochrane Central. The search used keywords including X-linked hypophosphatemia, X-linked hypophosphatemic rickets, familial hypophosphatemia, XLH, burosumab, anti-FGF23 antibody, active vitamin D, calcitriol, alfacalcidol, and phosphate.

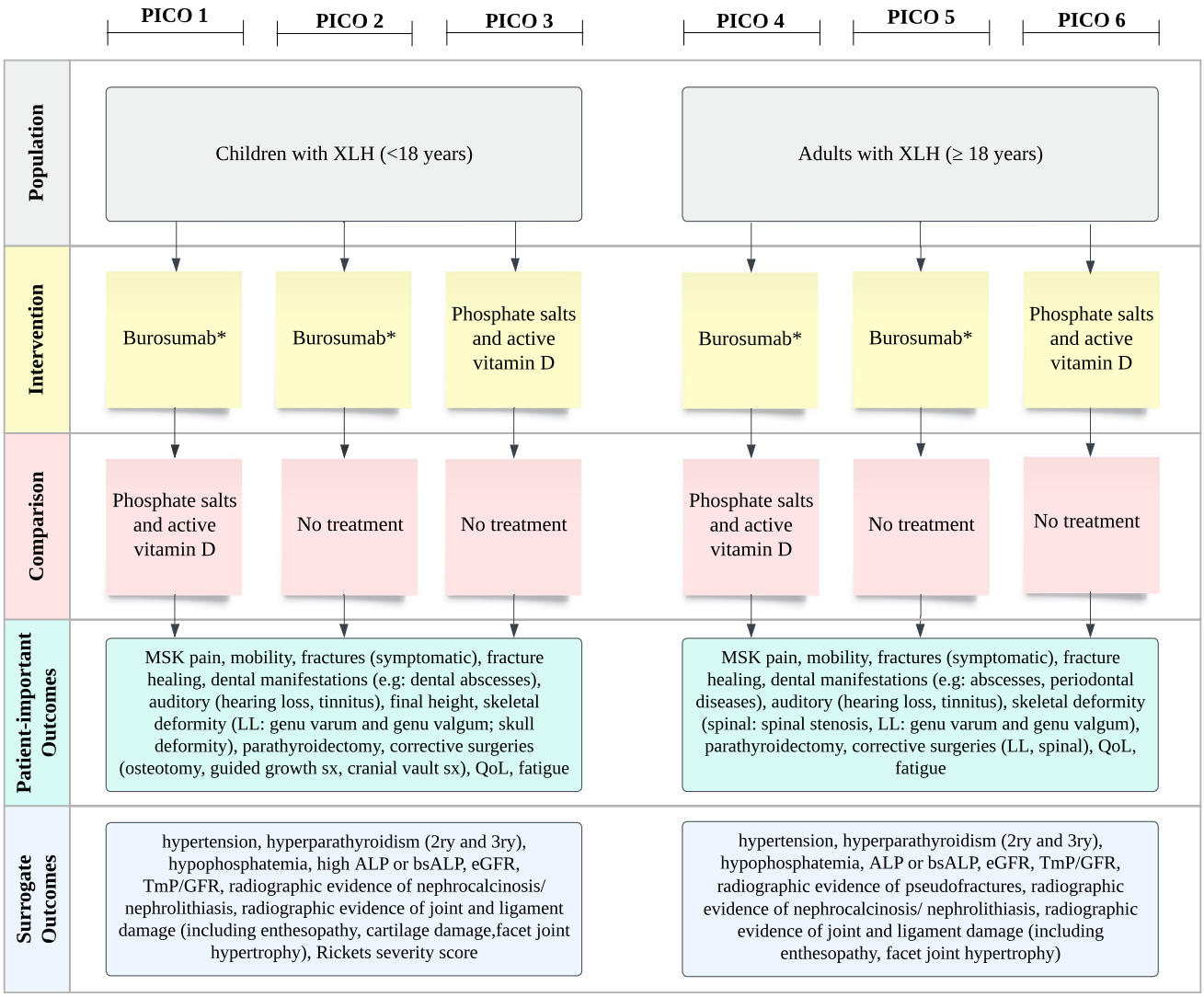

Fig. 3 PICO Questions used for GRADEd Recommendations. *ALP* alkaline phosphatase; *BsALP* bone-specificalkaline phosphatase; *eGFR* estimated glomerular filtration rate; LL: lower limb; MSK: musculoskeletal; QoL: Quality of life; *Sx* surgery; *TmP/GFR* Tubular maximum phosphate reabsorption adjusted for glomerular filtration rate; *XLH* X-linked hypophosphatemia

Eligibility and risk of bias assessment

The PICO questions focused on evaluating the efficacy of various medical interventions in patients with XLH, particularly on patient-important outcomes, which are variables that reflect how a patient feels, functions or survives. They also examined the efficacy of medical intervention compared to no treatment, as outlined in Fig. 3. The eligibility criteria primarily included randomized controlled trials (RCTs) and in cases where RCTs were unavailable, observational studies were included.

To assess the risk of bias in RCTs, the Cochrane risk-of-bias tool, modified by the CLARITY group at McMaster University was used (see Appendix A) [4]. This involved evaluating criteria such as random sequence generation, allocation concealment, blinding of participants, healthcare providers, outcome adjudicators and missing outcome data. Each criterion was judged as definitely or probably representing a low risk of bias, or definitely or probably indicating a high risk of bias.

The risk of bias in observational studies was assessed using the modified Ottawa–Newcastle scale across eight domains: selection bias, exposure to intervention, assessment of outcome measurements at the start and end of the trial, evaluation of prognostic features, appropriate adjustment of prognostic imbalances, adequacy of follow-up, and similarity of intervention between groups (see Appendix B).

Evaluating the certainty of evidence

The methodology team assessed the certainty of evidence in the XLH treatment systematic reviews using GRADE working group criteria. Each outcome was graded individually.

Conducting meta-analyses

Due to the limited number of eligible studies, only one meta-analysis was completed and this was for adults evaluating conventional therapy versus no treatment with serum phosphorus as the outcome (PICO number 6 in Fig. 3). In children, a meta-analysis was not possible due to insufficient data as we identified only one eligible RCT [5]. Although a post-hoc analysis addressing different outcomes from the same trial was available, due to this mismatch, a comprehensive meta-analysis could not be conducted [6].

Outcomes of interest

The guideline IWG members, along with a patient partner and input from the methodology team identified 12 patient-important outcomes in children and 11 in adults. They have also identified 11 surrogate outcomes in children and 9 in adults as listed in Fig. 3. The methodology team applied the GRADE approach to assess the certainty of evidence for all outcomes and generated summary of findings tables.

Summary-of-findings (SoFs) tables

We generated five SoF tables that informed the GRADEd treatment recommendations. These tables provide a detailed breakdown of each outcome, outlining the measurement method, follow-up duration, mean difference, and the certainty of evidence. See the seven elements described in SoFs tables listed in Box 1 [7]. The SoFs also include a plain language summary to describe the quality of evidence associated with each outcome [7, 8]. To generate the SoF, we used a specific format provided by MAGICApp, which is a collaborative, web-based content management system for authoring and publication (http://help.magicapp.org/knowledgebase).

The five SoFs generated from our systematic reviews are discussed in greater detail in separate publications [9, 10].

Box 1 Seven elements of a Summary of Findings table

1. A list of all important outcomes, both desirable and undesirable;
2. A measure of the typical burden of these outcomes (e.g. control group, estimated risk);
3. A measure of the risk in the intervention group or, alternatively or in addition, a measure of the difference between the risks with and without intervention;
4. The relative magnitude of effect;
5. Numbers of participants and studies addressing these outcomes;
6. A rating of the overall confidence in effect estimates for each outcome (which may vary by outcome); and possibly;
7. Comments.

Box 1 List of the Seven elements of Summary of Findings Table

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Recommendation direction and strength

We used a structured approach to form and categorize the GRADEd recommendations to either being strong, conditional or weak. The strength of recommendations depended on several factors including the balance between the positive and negative consequences of an intervention, the certainty of evidence, patient values and preferences, as well as considerations of feasibility, acceptability, and equity. In our guidelines, strong recommendations were expressed as "We recommend" and received a strong grade when the panel was confident that the desirable effects of the intervention outweighed the undesirable ones. On the other hand, conditional recommendations were structured when the panel concluded that the desirable effects of the intervention probably outweigh the undesirable effects, though there is some uncertainty. Weak recommendations were expressed as "We suggest", attributed either to low certainty evidence or to a close balance between the desirable and undesirable effects (see Table 1).

Table 1 Examples of desirable and undesirable outcomes

Desirable outcomes	Undesirable outcomes
Increase longevity	Decrease longevity
Reduction in morbid events intervention designed to prevent	Immediate serious complications (typically for surgical therapies)
Resolution of symptoms	Short-term relativity minor side effects
Improved quality of life	Long-term rare serious adverse events
Decreased resource use	Impaired quality of life
	Inconvenience/hassle
	Increase resource use

Reproduced with permission from J. Andrews et al.[2]

Survey development to address monitoring practices among experts treating patients with XLH

There are limited data on best monitoring strategies for patients with XLH. The methodology team along with input from expert clinicians and dental colleagues created a survey to assess practice amongst experts involved in the care of patients with XLH. We adapted the structure of the survey from a recent study on monitoring patients with chronic hypoparathyroidism [11]. The survey was categorized into four groups (children, adults, pregnant/lactating women, and patients with dental complications), and was distributed via SurveyMonkey (https://www.surveymonkey.com/). It covered clinical assessment of newly diagnosed patients with XLH and follow-up monitoring practices. The survey was sent to all members of the IWG in March 2023, we followed up with reminders and contacted respondents for missing information.

We conducted a second round of the survey for some of the questions that panel members felt strongly should be re-evaluated for clarification which included frequency of laboratory measurements in children treated with burosumab, documentation of fracture history in adults and children, inquiry about family history in all patient populations, baseline hand X-rays to assess for signs of rickets, and baseline bone mineral density in adults. The panel members finalized the recommendations after several meetings. The consensus was considered achieved when 80% or more of respondents performed the clinical, biochemical, or radiological assessments in at least 80% of their patients at least 80% of the time. The recommendations derived from the survey are GRADEd, weak recommendations and are based on very low-certainty evidence.

Values and preferences

The IWG considered patients' values and preferences in all recommendations. They also considered the input and perspectives of patients in the process of creating the guidelines through the patient representative. The panel specifically based their judgment on patient-important outcomes as opposed to surrogate outcomes.

Costs, feasibility, acceptability, equity

The panel considered equity and feasibility while constructing the recommendations which included both children and adults.

Finalizing the recommendations

Our objective by the end of the guideline process was to achieve consensus on both GRADEd and non-GRADEd recommendations. After completion of the systematic reviews, the steering committee of the guidelines, with input from the methodology team, drafted the GRADEd treatment recommendations which were then presented at three consecutive meetings to achieve consensus amongst members of the IWG. Our GRADEd monitoring recommendations were based on a rigorous expert clinical practice survey, where consensus was defined as parameters practiced by 80% of respondents on at least 80% of their patients, 80% of the time. These recommendations are weak because they were based on a clinical practice survey and offered very low-certainty evidence. Voting was not implemented and the panel agreed on the wording, direction and strength of the GRADEd recommendations.

Our non-GRADEd treatment and pregnancy recommendations were drafted by the steering committee and presented at the IWG meetings, where consensus was achieved over three virtual meetings. All suggested changes by the IWG members were taken into consideration, and edited drafts were sent out to all of the experts for ongoing feedback. The dental team from the IWG drafted the non-GRADEd dental recommendations, attaining consensus before presenting them to the entire IWG, who also agreed on the recommendations.

The panel formulated 14 non-GRADEd management recommendations in children and 16 in adults, one recommendation for diagnosis, 8 for pregnancy care, and 5 for dental care in children and adults, all of which had achieved consensus among the IWG members.

Disclosing and managing conflicts of interest

The IWG members voluntarily participated in developing the guidelines without receiving any financial compensation. The panelists disclosed their conflicts of interest in the manuscripts co-authored by them. The disclosure form is included in Appendix C. Some members disclosed industry consultancy and advisory board memberships, and their involvement was not excluded. The calcium disorders clinic at McMaster University, Canada, solely funded these guidelines. No funds were received from any pharmaceutical partners, and they had no influence on the guideline outcomes.

Internal and external presentations

The recommendations were presented internally among the IWG members and achieved consensus. We also obtained external validation by sharing the guidelines with numerous national and international societies involved in the care of individuals with rare bone diseases. Their endorsements were obtained by circulation of the guidelines for feedback among their members and their feedback was incorporated into the final manuscripts for both adults and pediatrics. To date, the guidelines have been endorsed by the following societies and associations: The American Society for Bone and Mineral Research (ASBMR), the Argentinian society, the Brazilian Association of Bone Assessment and Osteometabolism, 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 Disorders (ERN BOND), the French dental association, the International Society of Children's Bone Health (ISCBH), the Irish Endocrine Society (IES), the German Society of Endocrinology, the German Society of Osteology, the Japanese Society for Bone and Mineral Research (JSBMR), the Korean Society for Bone and Mineral Research (KSBMR), the Korean Endocrine Society (KES), the Kuwait Academy of Rare Diseases (KARD), the Pediatric Endocrine Society (PES) and the Patient Care Societies—Canadian XLH Network and XLH Denmark.

Limitations

The guideline process involved four systematic reviews addressing the management of XLH. Due to the limited evidence and available literature, we were only able to formulate 5 GRADEd management recommendations involving the use of burosumab (3 for adults and 2 for children). We were unable to formulate any GRADEd recommendations regarding the use of conventional therapy (phosphate salts and active vitamin D), nor were we able to develop recommendations for lack of treatment, due to the absence of good evidence, for either, with impact on patient-important outcomes.

Plans for updating

The current IWG members or their successors intend to revise the recommendations after determining the extent to which new data warrants a revision of the recommendations following a systematic review of the published literature.

Appendix

Appendix A: Modified Cochrane risk-of-bias tool.
https://acrobat.adobe.com/id/urn:aaid:sc:AP:24be0e90-d152-437e-afb8-22bdb7c85009

Appendix B: Modified Ottawa–Newcastle scale.
https://acrobat.adobe.com/id/urn:aaid:sc:AP:7670c8c0-3ed6-4ea6-b3a1-e51682664f20

Appendix C: Clinical Practice Guideline Conflict of Interest Form.
https://acrobat.adobe.com/id/urn:aaid:sc:AP:4804c20c-2e74-4cc9-b137-b7050852f795

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Author contributions Design/conceptualization of project: DSA, AAK, RM, GG. Data acquisition, review, analysis, methodology: DSA, AAK, RM, GG. Project administration, including acquisition of funding: AAK. Original drafting and preparation of manuscript: DSA, RM, GG. Review/editing of manuscript: DSA, AAK, RM, NMA, MLB, TOC, CC, EAI, SJdB, PF, AM, HAA, RTA, FA, SSBN, MBD, MCS, RKC, KD, GF, SF, CG, PG, CoG, ChG, SH, MKJ, SK, AK, AL, WFL, EML, CM, EM, AP, YR, HS, LT, LMW, GG.

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Data availability The data supporting the results of this study were obtained from publicly available sources. We are pleased to share the data upon a reasonable request made to the corresponding author.

Declarations

Conflict of interest Steering Committee: DSA: none; AAK: Speaker, advisory board (Alexion, Amgen); Speaker, advisory board, research funding (Ascendis); Advisory board, research funding (Takeda); Re-

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