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Glucocorticoid-Associated Osteonecrosis in Children with Acute Lymphoblastic Leukemia: Risk Factors, Diagnosis, and Management: A Narrative Review

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ABSTRACT

Introduction. Osteonecrosis (ON) is a disabling complication of childhood acute lymphoblastic leukemia (ALL) therapy, especially in adolescents. Glucocorticoid exposure is central to its development, but individual susceptibility and other treatment-related factors also contribute. MRI enables early detection, although prediction of lesion progression and optimal management remain challenging.

Aim. To summarize current evidence on glucocorticoid-associated ON in childhood ALL, focusing on risk factors, diagnosis, prevention, management, and long-term outcomes.

Material and methods. Narrative, non-systematic review of English-language publications identified in PubMed/MEDLINE and Google Scholar from January 2000 to September 2026. Cohort and case-control studies, randomized trials, systematic reviews, meta-analyses, guidelines, and consensus statements were considered, prioritizing pediatric ALL and recent evidence.

Results. Age ≥10 years and adolescence are the most consistent risk factors. Sex, glucocorticoid schedule and exposure, asparaginase, treatment intensity, metabolic abnormalities, and genetic susceptibility may further modify risk. MRI is the most sensitive method for early and multifocal disease, but lesion evolution is heterogeneous and evidence does not support universal screening. Intermittent dexamethasone scheduling may reduce ON risk in selected settings. No universally accepted management pathway exists; many lesions remain stable or resolve, whereas advanced articular disease may lead to collapse, surgery, and persistent functional impairment.

Conclusions. A risk-adapted strategy combining clinical surveillance, selective MRI, optimized treatment exposure, rehabilitation, and multidisciplinary care appears most appropriate. Prospective studies are needed to identify lesions at highest risk of progression and determine whether earlier intervention can prevent collapse and long-term disability.

Key words: acute lymphoblastic leukemia; ALL; glucocorticoids; osteonecrosis; magnetic resonance imaging; child

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy and accounts for the majority of acute leukemias diagnosed in children. Advances in risk-adapted multi-agent therapy and supportive care have transformed its prognosis, with five-year survival now exceeding 90% [1,2]. As survival has improved, the goals of contemporary ALL therapy have expanded beyond cure toward minimizing treatment-related morbidity, preserving physical function and quality of life throughout survivorship. Musculoskeletal and endocrine disorders remain important components of late ailments among modern ALL survivors despite reductions in other severe treatment-related sequelae [2].

Dexamethasone and prednisone are indispensable glucocorticoids in ALL therapy because of their potent antileukemic activity. Their administration, however, is associated with clinically important toxicities, including osteonecrosis (ON) [1,3,4]. ON is among the most disabling musculoskeletal complications of pediatric ALL treatment, with risk rising sharply after approximately 10 years of age [3,5-7]. The hips and knees account for much of clinically significant disease, while multifocal skeletal involvement is common [8-10]. Clinical manifestations range from asymptomatic abnormalities detected only by magnetic resonance imaging (MRI) to persistent pain, restricted movement, gait disturbance, subchondral collapse, secondary joint degeneration, and severe functional impairment [4,11,12]. Extensive femoral-head disease can progress to joint destruction and arthroplasty during adolescence or early adulthood [4,10,11].

The consequences extend beyond radiographic abnormalities. Survivors with ON demonstrate deficits in strength, flexibility, mobility, endurance, and physical quality of life, with the greatest impairment observed in patients with severe hip disease requiring surgery [13-15]. These findings support long-term physical function as a clinically meaningful outcome alongside structural joint preservation.

Although glucocorticoid exposure is central to ON development, the condition is multifactorial. Age and skeletal maturation, glucocorticoid exposure and scheduling, asparaginase, treatment intensity, metabolic disturbances, body composition, and genetic susceptibility all contribute to individual risk [3,6,16-21]. MRI-detected ON has also been observed before chemotherapy, indicating that treatment exposure alone does not explain every lesion [22]. The term glucocorticoid-associated osteonecrosis therefore better reflects the interaction between treatment and host susceptibility rather than the more deterministic term “glucocorticoid-induced” osteonecrosis.

This review addresses three related clinical questions: Which children are at greatest risk of Osteonecrosis? What is the role of MRI in detecting early or asymptomatic lesions? How can osteonecrosis be detected, prevented, and managed to minimize long-term functional morbidity? Particular emphasis is placed on diagnostic strategies, prevention, management, and long-term functional consequences, including the balance between early detection and overdiagnosis and between toxicity reduction and preservation of antileukemic efficacy.

2. Literature Search Strategy

This narrative review was conducted to identify and synthesize current evidence on glucocorticoid-associated osteonecrosis in children and adolescents with ALL. Literature searches were performed in the PubMed/MEDLINE and Google Scholar databases.

The search covered publications from January 2000 to September 2026, allowing recent evidence to be prioritized while retaining older landmark studies relevant to the epidemiology, pathogenesis, diagnosis, prevention, and management of ON. The search was restricted to English-language publications. Reference lists of relevant primary studies, systematic reviews, and narrative reviews were additionally hand-searched to identify further eligible publications.

Search terms included combinations of “acute lymphoblastic leukemia,” “acute lymphocytic leukemia,” “child,” “children,” “adolescent,” “pediatric,” “paediatric,” “osteonecrosis,” “avascular necrosis,” “glucocorticoids,” “corticosteroids,” “dexamethasone,” “prednisone,” “asparaginase,” “risk factors,” “magnetic resonance imaging,” “MRI,” “screening,” “treatment,” “management,” “surgery,” “functional outcome,” “rehabilitation,” and “quality of life.” Boolean operators AND and OR were used to refine searches.

The review included prospective and retrospective cohort studies, case-control studies, randomized controlled trials, systematic reviews and meta-analyses, and relevant clinical guidelines or consensus statements. Priority was given to studies specifically examining pediatric ALL and publications from 2021–2026. Older studies were retained when they represented landmark trials, large prospective cohorts, or important evidence regarding glucocorticoid exposure, MRI screening, long-term outcome, or ON management. Primary studies and systematic reviews were prioritized for evidentiary claims, while narrative reviews were used primarily to contextualize findings and identify relevant primary literature. Case reports, conference abstracts, non-English publications, and studies without clinically relevant information on ON were excluded. Evidence from patients with other diseases was considered only when pediatric ALL-specific evidence was insufficient and the limits of extrapolation were clinically relevant.

3.Glucocorticoid-Associated Osteonecrosis in Childhood Acute Lymphoblastic Leukemia: Current Evidence

3.1. Glucocorticoid Therapy in Childhood Acute Lymphoblastic Leukemia

Glucocorticoids are essential components of contemporary childhood ALL therapy because of their potent lympholytic effects and contribution to disease control. Prednisone/prednisolone and dexamethasone are incorporated into induction and re-intensification phases, and some protocols use additional glucocorticoid pulses during later treatment. Although dexamethasone offers greater glucocorticoid potency and superior central nervous system penetration, these therapeutic properties are accompanied by clinically relevant toxicity, including ON [6,16,17].

The relationship between glucocorticoid exposure and ON depends not simply on cumulative dose but also on the type, timing, duration, and pattern of exposure. In the CCG-1961 randomized cohort trial, alternate-week dexamethasone during delayed intensification significantly reduced symptomatic ON compared with continuous administration in patients aged ≥10 years with rapid early response [16]. The difference was substantial despite intensive antileukemic therapy, suggesting that uninterrupted exposure may be especially detrimental. Subsequent COG AALL0232 findings similarly demonstrated a strong age-treatment interaction and contributed to protocol modifications involving alternate-week dexamethasone during delayed intensification [6].

Pharmacokinetic variability further modifies individual exposure. Reduced dexamethasone clearance and consequently greater systemic exposure have been associated with severe ON [17]. A large national database analysis across glucocorticoid-treated pediatric conditions also found older age, dexamethasone use, and a greater number of glucocorticoid treatment days to be independently associated with ON; ALL itself was by far the strongest disease-associated risk factor in that heterogeneous population [23]. Although these data are not specific to ALL treatment protocols, they provide supportive evidence that age, glucocorticoid type, and duration of exposure influence ON risk [23].

Glucocorticoid toxicity also occurs within a multidrug regimen. Concurrent asparaginase may increase systemic dexamethasone exposure and contribute to abnormalities in coagulation and lipid metabolism [17,18,24]. Consequently, the effect of changing steroid

scheduling may depend on the surrounding regimen. In DCOG protocols, shorter dexamethasone pulses did not independently reduce ON when treatment included intensified PEG-asparaginase exposure [18]. Conversely, NOPHO ALL2008 data found no association between maintenance of methotrexate or 6-mercaptopurine metabolite levels and symptomatic ON [25]. These observations indicate that glucocorticoid exposure should be considered in the context of the entire treatment regimen rather than as an isolated toxicity determinant.

3.2. Pathogenesis of Glucocorticoid-Associated Osteonecrosis

ON in childhood ALL is generally understood as the consequence of inadequate intraosseous blood supply followed by ischemic injury and death of bone and marrow cells. Glucocorticoids contribute through interacting vascular, metabolic, and cellular mechanisms rather than a single pathway. Steroid exposure can promote endothelial dysfunction, vasoconstriction, hypercoagulability, and impaired fibrinolysis, thereby increasing the likelihood of microvascular obstruction. Simultaneously, glucocorticoid-driven adipogenesis and hypertrophy of marrow adipocytes may increase intraosseous pressure, compress venous sinusoids, and further compromise perfusion. Lipid accumulation may additionally contribute to endothelial injury or intravascular obstruction [24,26,27].

Experimental evidence supports vascular injury as an early event. In murine models, epiphyseal arteriopathy characterized by luminal occlusion and loss of vascular cells precedes or accompanies marrow and osteocyte necrosis [24,27]. This sequence provides a plausible explanation for the particular vulnerability of epiphyseal and subchondral regions, where limited collateral blood supply may make recovery from microvascular injury more difficult.

Glucocorticoids also exert direct effects on skeletal cells. They promote osteocyte apoptosis, suppress osteoblast differentiation and function, and shift mesenchymal stem-cell differentiation toward adipogenic rather than osteogenic pathways [26,27]. These effects impair the capacity to repair ischemic bone. Once necrosis has occurred, reparative tissue may be unable to restore the mechanical integrity of subchondral bone before physiological loading produces microfracture, deformation, and eventual articular collapse.

The striking age distribution suggests that puberty itself modifies susceptibility. Potential

explanations include rapid skeletal growth, hormonal changes, epiphyseal maturation and closure, increased metabolic demands, and age-related alterations in bone vascular physiology. Contemporary Austrian population-based data support a strong pubertal pattern: symptomatic ON occurred much more frequently among patients aged 10–18 years, with an earlier peak among girls than boys [7]. These observations are consistent with, but do not prove, a biological role for pubertal hormonal and skeletal maturation [7].

Metabolic abnormalities may further amplify vascular injury. Dexamethasone exposure has been associated with higher cholesterol and lower albumin levels, while poor dexamethasone clearance has been linked to severe ON [17]. Glucocorticoids and asparaginase both influence lipid metabolism, and severe hypertriglyceridemia has been associated with increased ON risk [28,29]. However, whether dyslipidemia is a causal mediator, a marker of high treatment exposure, or both remains uncertain.

Finally, marked interindividual variability indicates an important contribution from inherited susceptibility. Pharmacogenomic studies have identified associations involving pathways related to lipid homeostasis, apoptosis, coagulation, angiogenesis, and bone biology. Variants involving ACP1–SH3YL1, PGAP2, BCL2L11, THBD, CD93, and other loci have been implicated [17,19-21]. However, genetic associations differ across protocols, ancestries, and phenotype definitions, and no genomic marker currently has sufficient validation for routine clinical risk prediction.

Overall, ON appears to result from interaction among glucocorticoid exposure, microvascular injury, altered coagulation and lipid metabolism, marrow adiposity, impaired bone repair, concomitant antileukemic therapy, skeletal maturation, and genetic susceptibility.

3.3. Epidemiology and Natural History

Reported ON frequency varies substantially according to age distribution, treatment protocol, diagnostic definition, follow-up duration, and whether ascertainment is restricted to symptomatic disease or includes systematic MRI screening. A systematic review reported frequencies ranging from approximately 1% to 39%, with ON usually developing during the first several years of ALL therapy [30]. Systematic MRI studies report substantially higher frequencies because they identify asymptomatic lesions that would remain undetected by symptom-based surveillance [3,11,12,17].

Contemporary cohorts illustrate this heterogeneity. Imaging-confirmed ON occurred in 12.2% of patients in COG AALL0232 [6], symptomatic ON in 4.5% of a Chinese pediatric cohort [31], and serious ON defined as Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3 in 1.7% of a Canadian population-based cohort [5]. The Austrian ALL-BFM population-based analysis identified symptomatic ON in 73 of 1,127 children, corresponding to a five-year cumulative incidence of approximately 7% and a median time to diagnosis of 1.64 years [7]. Incidence differed markedly by age, reaching 22% among patients aged 10–18 years compared with 2% among children aged 1–9 years [7].

The hip and knee account for much of clinically relevant ON, although their relative prominence depends partly on how the disease is ascertained. MRI-based cohorts frequently identify numerous knee lesions and multifocal abnormalities, whereas femoral-head involvement has disproportionate importance because of its association with collapse and arthroplasty [8,10,11,30]. ON should therefore not be conceptualized solely as a disease of the hip. In the recent NOPHO ALL2008 follow-up study, 235 lesions were identified among 37 patients, with a mean of 6.4 lesions per patient and involvement of 15 anatomical sites [10].

Natural history is similarly heterogeneous. Lesions affecting convex articular surfaces have shown greater deterioration than many concave-surface or diaphyseal abnormalities [8]. Earlier prospective DCOG follow-up found that 25% of lesions improved radiologically, 54% remained stable, and 21% progressed [33]. In the more recent NOPHO cohort, 55% of serially imaged lesions remained stable, 35% resolved completely, 8% improved, and only 2% progressed [10]. Nevertheless, 11 patients ultimately developed Niinimäki grade 5 ON, representing joint-surface collapse or destruction [10]. Older age and female sex were associated with a lower likelihood of spontaneous resolution, while HSCT was associated with advanced collapse at presentation [10].

ON should therefore be viewed as a spectrum from transient or clinically silent abnormalities to progressive subchondral disease. The central clinical problem is not simply detecting ON, but distinguishing lesions likely to remain stable from those likely to result in pain, collapse, surgery, and long-term functional impairment.

3.4. Risk Factors for Osteonecrosis

ON in childhood ALL is best understood as a multifactorial toxicity resulting from

interactions between patient susceptibility, disease characteristics, and treatment exposure. Numerous associations have been described, but age and adolescence remain the most reproducible predictors across contemporary protocols [5-7,16-18,30,33].

3.4.1. Patient-Related Factors

Age and pubertal status represent the strongest and most consistent determinants. Children aged ≥10 years have markedly higher ON risk, with incidence generally rising further through adolescence [5,6,16-18,30,33]. In the Canadian population-based study, age ≥10 years independently increased the risk of serious ON approximately sevenfold [5]. The recent Austrian ALL-BFM analysis strengthens this observation: five-year symptomatic ON incidence was 22% among patients aged 10-18 years compared with only 2% among children aged 1–9 years, and age was the only statistically independent risk factor in multivariable analysis [7]. Using a 15-year threshold, incidence increased further to approximately 25% among patients aged 15-18 years [7].

Female sex has also been associated with increased ON risk in several cohorts [5,16,33], although findings are not uniform. It remained independently associated with serious ON in the Canadian population-based analysis [5], whereas the Austrian study did not demonstrate an independent sex effect [7]. Age-specific Austrian data showed an earlier ON peak among girls than boys, supporting the possibility that pubertal timing rather than sex itself explains part of the apparent association [7]. Furthermore, female sex was associated with reduced spontaneous lesion resolution in the Finnish NOPHO ALL2008 follow-up cohort [10].

The contributions of BMI and body composition remain inconsistent. Increased body mass could theoretically increase mechanical loading of vulnerable weight-bearing joints and may correlate with marrow adiposity and metabolic abnormalities. Higher BMI has been identified as a possible risk factor in some studies [12,30], but other large cohorts have not demonstrated an independent association [5,18,33]. In the Austrian cohort, height, weight, and BMI were associated with ON in univariate analysis but lost significance after adjustment, suggesting substantial confounding by age and pubertal development [7].

Ethnicity and ancestry have similarly produced inconsistent findings. White/non-Hispanic ancestry has been associated with greater risk in some cohorts, while other studies have not confirmed race as an independent determinant [5,30,32,34]. Genetic ancestry may therefore

be more useful as a proxy for underlying genomic differences than as an independent clinical risk factor.

Increasing evidence supports inherited susceptibility. Associations have been reported involving ACP1–SH3YL1, GRIN3A, BMP7, PROX1-AS1, NWD2, and other loci [17,21,30]. More recently, variants involving PGAP2, BCL2L11, and ACP1–SH3Y remained associated with bone toxicity across changing DFCI protocols [19]. However, effect sizes and phenotypes vary according to treatment exposure and study population, and pharmacogenomic screening is not yet sufficiently validated for routine care [12,19-21

3.4.2. Disease-Related Factors

Higher-risk ALL classification and T-cell immunophenotype have been associated with ON in several cohorts, although the extent to which this reflects disease biology is uncertain [5,17,32]. In the Canadian study, T-ALL and high-risk disease were associated with serious ON in univariate analysis but did not remain independent predictors after adjustment [5].

The Austrian population-based analysis provides similar evidence. Symptomatic ON incidence was higher among T-ALL than B-ALL patients and increased progressively from standard- to medium- and high-risk treatment groups, but these associations disappeared in multivariable analysis [7]. Patients with T-ALL or higher-risk disease were generally older and received more intensive therapy, including greater glucocorticoid exposure [7]. Disease-related associations should therefore be interpreted cautiously because they may largely reflect age and treatment intensity rather than an intrinsic osteonecrotic effect of leukemia subtype.

3.4.3. Treatment-Related Factors

Glucocorticoid exposure remains the principal treatment-related factor, but type, systemic exposure, cumulative treatment, and scheduling all appear relevant. Dexamethasone has been associated with higher ON rates than prednisone in selected studies, although this relationship is not consistent across protocols [6,33]. The Austrian cohort, for example, found no significant difference in symptomatic ON according to dexamethasone versus prednisone during induction [7]. This reinforces the concept that cumulative exposure, duration, pharmacokinetics, age, and scheduling may be more clinically relevant than the

glucocorticoid molecule considered in isolation.

Continuous glucocorticoid exposure is particularly important. Alternate-week dexamethasone during delayed intensification approximately halved symptomatic ON incidence in older children in CCG-1961 [16]. Pharmacokinetic data further demonstrate that impaired dexamethasone clearance and high systemic exposure increase susceptibility to severe ON [17]. Broader pediatric glucocorticoid data also associate ON with older age, dexamethasone exposure, and longer cumulative treatment duration [23], although these findings should be considered supportive rather than ALL protocol-specific.

Asparaginase may potentiate glucocorticoid toxicity through effects on dexamethasone pharmacokinetics, coagulation, and lipid metabolism [17,18,24]. However, the magnitude of this interaction differs between protocols. Likewise, evidence supporting methotrexate as an independent clinical risk factor remains weak: NOPHO ALL2008 found no association between maintenance methotrexate or mercaptopurine metabolite exposure and symptomatic ON [25].

Greater overall treatment intensity frequently correlates with ON risk [6,7,17,18]. HSCT represents a particularly complex exposure because transplantation is accompanied by additional glucocorticoid administration and multiple metabolic, vascular, inflammatory, and skeletal insults. HSCT was associated with serious ON in univariate analysis in the Canadian cohort [5], and recent Finnish data found a strong association between HSCT and

presentation with grade 5 joint collapse [10]. These observations support greater vigilance in transplant recipients but do not establish HSCT itself as an isolated causal factor. The principal patient-, disease-, and treatment-related factors associated with ON, together with their current clinical interpretation, are summarized in Table 1.

Table 1. Patient-, disease-, and treatment-related factors associated with osteonecrosis in childhood acute lymphoblastic leukemia

Domain	Factor	Evidence summary	Clinical interpretation
Patient-related	Age ≥10 years /	The most consistently	Strongest currently available clinical

	adolescence	reproduced risk factor across cohorts. Risk increases markedly after approximately 10 years of age and is highest during adolescence [5-7,16-18,30,33].	marker of ON susceptibility.
Patient-related	Pubertal maturation	The age distribution of ON and earlier peak observed in females support a possible contribution from pubertal skeletal and hormonal changes [7].	Likely contributes to adolescent susceptibility, although pubertal stage itself has been measured inconsistently.
Patient-related	Female sex	Associated with increased ON risk in several cohorts [5,16,33], but not independently significant in all studies [7]. Female sex was also associated with lower probability of spontaneous lesion resolution [10].	Relevant risk modifier, but less consistent than age.
Patient-related	BMI / body composition	Higher BMI has been associated with ON in some studies, but associations frequently weaken after adjustment for age and pubertal development [5,7,12,18,30,33].	Evidence is inconsistent; BMI should not currently be used as an isolated predictor.
Patient-related	Ethnicity / ancestry	Differences have been reported across populations, but race or ethnicity has not consistently	Clinical predictive value remains uncertain.

		remained independently associated with ON [5,30,32,34].	
Patient-related	Genetic susceptibility	Associations include variants involving ACP1–SH3YL1, PGAP2, BCL2L11, GRIN3A, BMP7, PROX1-AS1, THBD, CD93, and other loci [17,19-21].	Promising for future integrated risk prediction, but insufficiently validated for routine clinical use.
Disease-related	ALL risk group	Higher-risk groups show greater ON incidence in several cohorts, but associations frequently diminish after adjustment for age and treatment intensity [5,7].	Likely reflects treatment intensity more than an independent effect of leukemia biology.
Disease-related	T-ALL versus B-ALL	Higher crude ON incidence has been reported in T-ALL, but T-cell immunophenotype has not consistently remained an independent predictor [5,7].	Association appears substantially confounded by age and treatment intensity.
Treatment-related	Glucocorticoid type and systemic exposure	Associations between dexamethasone versus prednisone are inconsistent across protocols [6,7,33]. Reduced dexamethasone clearance and greater systemic exposure are associated with severe ON [17].	Exposure and pharmacokinetics appear more informative than drug identity alone.

Treatment-related	Continuous versus intermittent glucocorticoid exposure	Alternate-week dexamethasone during delayed intensification significantly reduced symptomatic ON compared with continuous exposure in CCG-1961 [16].	Best-supported modifiable treatment-related risk factor.
Treatment-related	Cumulative / prolonged glucocorticoid exposure	Longer exposure is associated with increased risk, although schedule and pharmacokinetics substantially modify this relationship [17,23].	Total exposure should be interpreted together with timing and treatment context.
Treatment-related	Asparaginase	Can alter dexamethasone exposure, coagulation, and lipid metabolism; clinical effects vary between protocols [17,18,24].	Probable treatment-context modifier rather than a uniform independent predictor.
Treatment-related	Methotrexate	Maintenance methotrexate metabolite exposure was not associated with symptomatic ON in NOPHO ALL2008 [25].	No evidence currently supports methotrexate reduction specifically for ON prevention.
Treatment-related	Overall treatment intensity	More intensive treatment is associated with higher ON risk in several cohorts [6,7,17,18].	Important contextual determinant that overlaps with glucocorticoid and asparaginase exposure.
Treatment-related	HSCT	Associated with serious ON in selected cohorts [5]	Supports increased clinical vigilance in transplant recipients;

		and with presentation with advanced joint collapse in recent NOPHO follow-up [10].	HSCT should not be interpreted as an isolated causal factor.

Abbreviations: ALL-acute lymphoblastic leukemia; BMI-body mass index; HSCT-hematopoietic stem-cell transplantation; ON-osteonecrosis. Table note: Evidence descriptors reflect consistency and quality of the available pediatric literature and do not represent a formal GRADE assessment.

3.5. Clinical Presentation and Consequences

3.5.1. Clinical Manifestations

Clinical presentation is highly variable and does not reliably indicate the extent of radiological disease. Early ON may remain entirely asymptomatic and be identified only on MRI, whereas symptomatic disease typically presents with persistent bone or joint pain, restricted range of motion, limping, reduced weight bearing, or gait disturbance [4,6,11,22].

In NOPHO ALL2008, pain was reported in 91% of symptomatic patients, limping in 49%, and reduced joint mobility in 46% [9]. However, absence of pain cannot exclude clinically relevant disease. MRI studies have repeatedly demonstrated asymptomatic lesions and hip ON may remain silent despite measurable impairment [11-13]. Consequently, reliance on symptoms alone inevitably underestimates radiological ON prevalence.

Symptoms may also be difficult to distinguish from other complications of ALL therapy. Bone pain, muscle weakness, vincristine-related neuropathy, steroid myopathy, reduced physical activity, and leukemia-related skeletal symptoms may overlap with early ON manifestations [4,12]. Persistent or progressive joint pain, especially when associated with gait disturbance or restricted movement after glucocorticoid-intensive treatment phases, should therefore prompt specific evaluation for ON.

3.5.2. Structural and Orthopedic Consequences

The prognosis of ON depends strongly on lesion size, anatomical location, involvement of the articular surface, and presence of subchondral structural failure [8,10,11,35-37]. Epiphyseal or subchondral lesions affecting weight-bearing surfaces are of greatest concern, because progression may produce microfracture, deformation, articular collapse, secondary osteoarthritis, and eventual joint destruction.

Kaste et al. demonstrated that extensive femoral-head ON involving at least 30% of the epiphyseal surface carries an unfavorable prognosis in adolescents; 19 of 40 extensive lesions in patients older than 10 years ultimately required total hip arthroplasty [11]. In contrast, many small, metaphyseal, or diaphyseal abnormalities have a substantially more benign course [8,12].

The recent NOPHO follow-up study reinforces the importance of distinguishing lesion presence from structural severity. Although most lesions were stable or resolved, nine patients already had Niinimäki grade 5 disease, indicating joint-surface collapse, at diagnosis, and 11 patients ultimately developed at least one grade 5 lesion [10]. Total joint arthroplasty was performed exclusively for grade 5 femoral-head ON, at a mean age of only 16.7 years [10]. Other joint-preserving procedures included osteotomy and drilling, with variable outcomes according to lesion severity [10].

ON is also commonly multifocal. Finnish NOPHO data showed a mean of 6.4 lesions per affected patient, while previous cohorts similarly identified involvement of multiple joints and skeletal regions [8-10]. Imaging and orthopedic assessment should therefore consider the possibility that clinically important disease extends beyond the initially symptomatic joint.

3.5.3. Functional Outcomes and Quality of Life

Structural outcome alone does not adequately describe the burden of ON. Persistent disease may impair walking, physical activity, participation, independence, and everyday activities [9,13,14,31-33,38]. In the prospective DCOG cohort, only 40% of affected patients became completely asymptomatic during follow-up; another 40% continued to experience symptoms interfering with function, and 20% had limitations affecting activities of daily living [33].

Long-term survivor studies demonstrate that these effects can persist well beyond completion of leukemia treatment. In the PETALE cohort, survivors with hip ON showed reduced hip external rotation and clinically relevant physical impairment and activity limitations [13]. Girard et al. reported worse physical functioning, bodily pain, general health, and overall physical quality-of-life scores among adult leukemia survivors with symptomatic ON [14]. Contemporary Danish data further identified severe ON requiring arthroplasty or causing persistent major functional impairment as the most frequent severe toxicity in ALL cohort [38].

The St. Jude Lifetime Cohort provides more detailed objective evidence regarding physical performance [15]. In 135 adult survivors of childhood leukemia or lymphoma with a history of symptomatic ON, survivors demonstrated deficits in dorsiflexion strength and performed worse than healthy controls on measures of flexibility, mobility, and overall physical performance [15]. The most clinically vulnerable subgroup consisted of survivors who had required surgery for hip ON. Compared with survivors without ON, these patients had lower dorsiflexion strength, reduced flexibility, and shorter six-minute walking distances; their mean six-minute walk distance was approximately 524 m compared with 572 m among survivors without ON [15]. Patients requiring hip surgery also had worse flexibility and endurance than survivors with ON who did not require hip surgery [15]. Importantly, the association between surgery and poor long-term performance should not be interpreted as evidence that surgery itself causes these deficits. Patients requiring surgery generally have more severe structural disease, and the St. Jude study was cross-sectional [15]. Nevertheless, the findings identify severe hip ON as a marker of substantial long-term rehabilitation needs. Strength, flexibility, endurance, mobility, pain, and participation should therefore be considered relevant outcomes in both clinical follow-up and future ON trials, rather than relying solely on MRI grade or arthroplasty as endpoints.

3.6. Diagnosis and Imaging

3.6.1. Clinical Assessment

Early diagnosis remains challenging because ON may be asymptomatic or present with nonspecific complaints common during ALL therapy. ON should be considered in patients with persistent joint or limb pain, limping, restricted range of motion, reduced weight

bearing, or otherwise unexplained deterioration in physical function, particularly among adolescents aged ≥10 years [4,7,12]. Symptoms occurring during or shortly after glucocorticoid-intensive phases deserve particular attention.

Clinical assessment alone cannot reliably exclude ON. Prospective MRI studies have demonstrated substantial numbers of asymptomatic lesions, and ON abnormalities have even been identified at ALL diagnosis before chemotherapy [11,22]. Conversely, nonspecific pain may occur without ON. Imaging is therefore essential when clinical suspicion persists.

3.6.2. Plain Radiography and Magnetic Resonance Imaging

Plain radiography is readily available and useful for evaluating established structural abnormalities but has limited sensitivity for early ON. Radiographic findings such as sclerosis, subchondral irregularity, flattening, or articular collapse generally occur later in the disease course, and normal radiographs cannot exclude early disease [4,35].

MRI is the preferred and most sensitive modality for early and multifocal ON [4,10,12,35]. It can detect abnormalities before radiographic structural failure and provides information regarding lesion location, extent, involvement of the articular surface, and subchondral integrity. These characteristics are more clinically informative than lesion presence alone.

MRI also demonstrates the multifocal nature of ON. Brivio et al. identified a median of six lesions on the first positive MRI [8], closely paralleling the recent NOPHO ALL2008 finding of a mean of 6.4 lesions per affected patient [10]. In the latter cohort, 235 lesions were identified among 37 patients and involved 15 different anatomical sites [10]. Such findings highlight the limitations of assuming that pain in a single joint represents the full extent of disease.

3.6.3. Radiological Classification and Prognostic Significance

Radiological assessment should characterize where the lesion is located, how large it is, whether it involves the epiphysis and weight-bearing articular surface, and whether subchondral damage or collapse is already present. Historically, inconsistent diagnostic and grading systems have limited comparison across studies. Niinimäki et al. found that many childhood leukemia studies either failed to report diagnostic methodology adequately or did

not use a standardized radiological classification [35].

The Niinimäki classification subsequently provided a reproducible, non-joint-specific system capable of grading lesions throughout the skeleton [36]. The more recent BLAST framework similarly emphasizes anatomical distribution across epiphyseal, metaphyseal, and diaphyseal regions [37], although additional prospective validation is required.

Clinically, lesion grade and anatomical location appear more important than simply counting abnormalities. Convex articular lesions have shown greater deterioration than many concave or diaphyseal lesions [8]. Recent Finnish follow-up found that almost all grade 5 lesions at final assessment affected convex surfaces, although progression was too uncommon to establish joint-surface geometry as an independent prognostic determinant [10]. Older age and female sex were associated with reduced probability of spontaneous resolution, while HSCT was associated with advanced collapse at presentation [10].

These findings reinforce that MRI should ideally provide prognostic information rather than a binary diagnosis. A small metaphyseal lesion far from the joint line has fundamentally different implications from extensive subchondral femoral-head ON in an adolescent.

3.6.4. Screening of Asymptomatic High-Risk Patients

Whether asymptomatic high-risk children should undergo routine MRI screening remains one of the central unresolved questions in ALL-associated ON.

The principal argument for screening is that MRI can detect extensive lesions before pain or collapse. In the prospective study by Kaste et al., early MRI identified extensive asymptomatic femoral-head ON with 84.1% sensitivity and 99.4% specificity [11]. Screening was dramatically more efficient among patients older than 10 years: only 4.4 joints had to be screened to identify one extensive lesion, compared with 198 joints in younger children [11]. Extensive lesions in older patients had an unfavorable subsequent course, with 19 of 40 ultimately requiring arthroplasty [11].

The opposing argument is that MRI identifies many abnormalities that do not progress. Earlier MRI cohorts already demonstrated spontaneous regression or persistent asymptomatic disease [3,12,17,22]. Recent NOPHO follow-up substantially strengthens this concern: among lesions with serial imaging, 35% resolved completely, 8% improved, 55% remained

stable, and only 2% progressed [10]. These data indicate that detecting ON does not automatically identify a lesion requiring intervention.

Universal screening may therefore lead to additional imaging, anxiety, activity restrictions, and potentially unnecessary interventions without proven improvement in long-term outcomes. MRI also carries greater cost and resource requirements than radiography and may require sedation in selected younger children [4]. At the same time, a purely symptom-triggered approach risks diagnosing extensive epiphyseal disease only after structural damage has progressed.

A third strategy-targeted MRI surveillance of high-risk adolescents-may offer a clinically rational compromise. Age ≥10 years is consistently associated with ON risk [5-7,16], and early detection in this group has a considerably greater diagnostic yield [11]. However, targeted surveillance should not be presented as established standard care until prospective studies demonstrate that identifying high-risk lesions earlier leads to an intervention capable of preventing collapse, surgery, or long-term functional disability. The clinically relevant question is therefore not simply whether MRI detects ON earlier, but whether MRI-guided early management changes outcome.

3.7. Prevention and Management

3.7.1. Prevention and Modification of Treatment-Related Risk

No intervention reliably prevents ON in high-risk children. The strongest preventive evidence concerns glucocorticoid scheduling rather than complete avoidance or indiscriminate dose reduction. In CCG-1961, alternate-week dexamethasone during delayed intensification reduced symptomatic ON in patients aged ≥10 years from approximately 17,0% to 8.7%, with an even greater difference among older adolescents [16].

However, this effect cannot automatically be generalized to all ALL protocols. DCOG data demonstrate that shorter glucocorticoid pulses do not necessarily reduce ON when accompanied by intensified PEG-asparaginase exposure [18]. The Austrian ALL-BFM study similarly found no major difference according to dexamethasone versus prednisone during induction, suggesting that overall exposure, schedule, pharmacokinetics, age, and treatment context may be more important than glucocorticoid type considered alone [7].

Any attempt to reduce glucocorticoid exposure must be balanced against its central role in leukemia control. Older patients simultaneously have greater ON susceptibility and frequently receive more intensive therapy because of less favorable disease characteristics. Consequently, the aim should be optimization rather than simple reduction of glucocorticoid treatment [12,16-18].

There is currently insufficient evidence to recommend reducing asparaginase or methotrexate specifically to prevent ON [25,39]. Similarly, although hyperlipidemia, hypertension, abnormal dexamethasone exposure, and other metabolic factors may identify vulnerable patients, correction of these abnormalities has not yet been demonstrated to reliably prevent ON [12,17,18,28,29]. Future prevention is therefore likely to depend on risk-stratified strategies integrating age, treatment exposure, metabolic phenotype, pharmacokinetics, and potentially genomic susceptibility.

3.7.2. Management of Asymptomatic and Early-Stage Disease

Once ON is detected, management becomes considerably less evidence-based. Small asymptomatic lesions, particularly those away from articular weight-bearing surfaces, may reasonably be managed with observation, clinical surveillance, activity modification, and serial MRI [4,12,39].

Recent natural-history evidence provides stronger support for caution against automatically treating every MRI abnormality. In the NOPHO ALL2008 follow-up cohort, the majority of lesions remained stable or resolved, whereas progression occurred in only a small minority [10]. This reinforces the importance of distinguishing a radiological lesion from clinically threatening ON. However, the same cohort also demonstrated irreversible grade 5 disease and arthroplasty in a subset, indicating that observation should be guided by lesion location, structural grade, symptoms, patient age, and other risk characteristics [10].

Large epiphyseal or subchondral lesions involving substantial portions of the weight-bearing surface deserve closer surveillance and early orthopedic input because their potential for collapse is considerably greater [4,11,12,39]. The optimal follow-up interval and threshold for intervention remain undefined.

3.7.3. Conservative Management and Rehabilitation

Symptomatic treatment generally aims to reduce pain while preserving mobility and preventing secondary physical deconditioning. Common approaches include analgesia, activity modification, individualized protected weight bearing, physiotherapy, and rehabilitation [4,12,39]. Crutches, walkers, orthoses, or other assistive devices may be useful when loading exacerbates pain or when imaging suggests structural vulnerability.

However, evidence that prolonged weight-bearing restriction prevents progression is weak [4,39]. Excessive unloading during prolonged ALL therapy may also worsen muscle weakness, endurance, bone health, and functional independence. Restriction should therefore be tailored to lesion site and severity rather than applied uniformly.

Physiotherapy should extend beyond maintenance of joint range of motion. Relevant goals include preserving or restoring muscle strength, gait quality, flexibility, balance, endurance, and participation in age-appropriate activities [4,15]. Long-term functional data provide a particularly strong rationale for this approach. Adult survivors with a history of ON show measurable deficits in physical performance, and those requiring hip surgery are especially vulnerable to persistent reductions in flexibility, ankle dorsiflexion strength, and walking endurance [15]. These findings suggest that rehabilitation may remain relevant well after acute ON management and even after cancer treatment has ended.

For patients undergoing surgery, structured postoperative and long-term rehabilitation deserves particular attention. Periodic reassessment of mobility, strength, flexibility, pain, and endurance may identify deficits that would otherwise remain unrecognized [15].

3.7.4. Pharmacological Approaches

No pharmacological treatment has demonstrated sufficient efficacy to become a universal standard for ALL-associated ON.

Bisphosphonates are the most extensively investigated pharmacological approach. A systematic review found improvement in pain and mobility in some treated children; however, progressive joint destruction still occurred in approximately 46% [40]. In a Finnish national cohort, pain improved in seven of ten patients, but lesions classified as Niinimäki

grade 5, representing established joint destruction, did not recover, and all grade 5 hip lesions required surgical treatment [41]. Recent NOPHO follow-up similarly illustrates the difficulty of attributing radiological improvement to bisphosphonate treatment. Six patients received bisphosphonates, usually for pain; several lesions improved or resolved, but the sample was too small and treatment indications too heterogeneous for causal assessment [10]. The high spontaneous resolution rate of untreated or variably treated lesions further complicates interpretation [10].

Other proposed treatments—including prostacyclin analogues, anticoagulants, lipid-lowering agents, and hyperbaric oxygen—are supported largely by small uncontrolled series or evidence extrapolated from non-ALL ON [4,12,39]. Preclinical zoledronic acid reduced ON when administered early in murine models but raised concern regarding possible impairment of antileukemic efficacy when combined with chemotherapy [42]. These observations emphasize that an intervention intended to prevent skeletal toxicity must also be shown to be oncologically safe. At present, evidence is insufficient to establish a universally effective pharmacological therapy for ALL-associated ON.

3.7.5. Surgical Management

Surgery is generally considered for progressive lesions at high risk of structural failure or for established symptomatic disease. The objective in early disease is preservation of the native joint for as long as possible, particularly in adolescents with decades of expected life ahead.

Core decompression is the most frequently discussed joint-preserving procedure for early-stage femoral-head ON without collapse and may be performed alone or with drilling, grafting, or cellular techniques [4,12,39]. However, much of the evidence supporting these approaches derives from adult non-oncologic ON. Pediatric ALL-specific studies remain small and heterogeneous, and differences in lesion stage and surgical technique make comparison difficult [4,12,39].

Selected osteotomies, osteochondral grafting, and other reconstructive approaches may be considered in specialist centers, but robust comparative evidence is lacking. Recent NOPHO observations again illustrate the importance of disease stage: drilling was associated with resolution of one grade 4 ankle lesion, whereas established grade 5 collapse did not resolve following joint-preserving procedures [10]. Such observational findings cannot establish

efficacy but are biologically consistent with the principle that joint preservation is more feasible before irreversible collapse.

Once substantial articular deformation and joint destruction are established, arthroplasty may become unavoidable. In the recent Finnish cohort, arthroplasty was performed exclusively for grade 5 femoral-head ON, at a mean age of 16.7 years [10]. Arthroplasty at such a young age carries major lifetime implications, including prosthetic wear, loosening, and probable revision surgery [4].

Long-term functional data add another perspective. In the St. Jude survivor cohort, 28 of 135 patients with ON had required surgery, most commonly involving the hip; patients with surgically treated hip ON had the poorest long-term strength, flexibility, mobility, and endurance [15]. Again, these outcomes likely reflect severity as well as treatment, but they underscore why preventing progression to collapse is a clinically meaningful objective.

3.7.6. Multidisciplinary Care and the Persistent Evidence Gap

Management should be individualized through close collaboration between pediatric hematology-oncology, orthopedic surgery, radiology, physiotherapy and rehabilitation, and pain-management services; endocrinology may also be relevant when bone health or metabolic abnormalities coexist [4,12]. Decisions must account simultaneously for lesion anatomy, symptoms, skeletal maturity, treatment phase, blood counts, infection risk, ongoing glucocorticoid requirements and long-term functional consequences.

There is currently no evidence-based standard management pathway once ON develops. A dedicated management review found that 12 of 14 pediatric ALL intervention studies provided only level 4–5 evidence and that no eligible randomized controlled intervention trials established a preferred approach [39]. The later therapeutic review similarly emphasized the lack of high-quality pediatric evidence and the need to identify high-risk precollapse lesions for prospective intervention trials [12]. More recent observational studies of bisphosphonates, MRI evolution, rehabilitation, and surgery improve understanding but have not resolved this fundamental limitation [10,15,40,41].

The contrast is therefore striking: clinicians can increasingly identify who is at risk and which MRI abnormalities appear dangerous, but evidence remains weak regarding what intervention should follow that information. Current preventive and therapeutic strategies,

together with their evidence base, major limitations, and proposed clinical roles, are summarized in Table 2.

Table 2. Prevention and management strategies for osteonecrosis in childhood acute lymphoblastic leukemia

Strategy	Evidence and observed effect	Key limitation	Current clinical role
Intermittent glucocorticoid scheduling	Alternate-week dexamethasone reduced symptomatic ON compared with continuous exposure in CCG-1961 [16].	Effect is treatment-context dependent and cannot be extrapolated unchanged to every ALL protocol [18].	Strongest clinical evidence for reducing ON risk through treatment modification.
Optimization of antileukemic exposure	Avoiding unnecessary prolonged glucocorticoid exposure is biologically and clinically rational [12,16-18].	Antileukemic efficacy must not be compromised.	Treatment should be optimized rather than indiscriminately reduced.
Metabolic monitoring / risk-adapted prevention	Hyperlipidemia and altered glucocorticoid pharmacokinetics are associated with ON susceptibility [17,28,29].	No metabolic intervention has been shown to reliably prevent ON.	Potential component of future individualized prevention strategies.
Observation and serial follow-up	Many MRI-detected lesions remain stable or resolve spontaneously [8,10,22].	A minority progresses to irreversible collapse, and reliable predictors of progression are lacking.	Appropriate for selected asymptomatic or structurally low-risk lesions.
Activity modification / protected weight	Can reduce pain and mechanical stress on affected weight-bearing joints	Evidence that unloading prevents structural progression is weak.	Should be individualized rather than routinely

bearing	[4,12,39].	Prolonged restriction can worsen deconditioning.	prolonged.
Physiotherapy and rehabilitation	Supports range of motion, strength, gait, flexibility, endurance, mobility, and participation [4,15]. Long-term deficits are documented in survivors with severe ON [13-15].	No standardized pediatric ALL-specific rehabilitation protocol has been validated.	Important supportive component during treatment and survivorship.
Bisphosphonates	Observational studies report improvement in pain and mobility in some patients [40,41].	Structural progression can continue despite treatment; established Niinimäki grade 5 lesions do not reverse [41].	Possible symptomatic therapy in selected patients; not established as disease-modifying treatment.
Other pharmacological approaches	Prostacyclin analogues, anticoagulant or vascular strategies, lipid-lowering approaches, hyperbaric oxygen, and other therapies have been explored [12,39].	Evidence is small, uncontrolled, extrapolated, or preclinical. Zoledronic acid also raised concern regarding antileukemic efficacy in experimental models [42].	No universally effective pharmacological treatment is established.
Core decompression / drilling	Intended to preserve joints before collapse; biologically most plausible in precollapse disease [4,12,39].	Pediatric ALL-specific evidence is limited and heterogeneous.	Consider only in selected high-risk lesions after specialist orthopedic assessment.
Other joint-preserving procedures	Osteotomy, grafting, osteochondral reconstruction, and	Evidence consists largely of small series without robust	Individualized specialist approach rather than standard

	related procedures can be considered for selected lesions [10,12,39].	comparator groups.	pathway.
Arthroplasty	Can restore function and relieve pain when irreversible articular destruction is present [4,10].	Adolescents face decades of implant use and potential revision surgery.	Salvage treatment for advanced collapse when native-joint preservation is no longer feasible.
Multidisciplinary care	Integrates leukemia treatment, imaging, orthopedic assessment, pain management, rehabilitation, and long-term functional surveillance [4,12,15].	No single evidence-based pathway defines the timing of each intervention.	Recommended framework for individualized management.

Abbreviations: ALL-acute lymphoblastic leukemia; MRI-magnetic resonance imaging; ON-osteonecrosis. Table note: Evidence supporting management after ON develops is substantially weaker than evidence regarding epidemiology and risk factors. Most pediatric intervention studies are observational, small, and heterogeneous; therefore, no universally accepted management pathway has been established [12,39-41].

4. Discussion

4.1. Clinical Risk Stratification

The evidence has become sufficiently consistent to distinguish between factors associated with developing ON and factors that may influence what happens after ON has developed. Age ≥10 years and adolescence are the clearest predictors of ON occurrence across contemporary cohorts [5-7,16-18,30,33]. Other variables including: female sex, treatment intensity, glucocorticoid exposure, asparaginase, metabolic abnormalities, and genetic susceptibility - modify risk less consistently [5,17-21,28,29]. Once ON is present, older age and female sex also appear to reduce the probability of spontaneous lesion resolution, while HSCT is associated with more advanced disease in selected cohorts [10].

No current model predicts clinically consequential ON with sufficient accuracy for routine

individualized decision-making [12,19-21]. Importantly, future prediction tools should not use MRI positivity alone as their endpoint. The clinically relevant target is a lesion likely to progress to subchondral collapse, persistent pain, surgery, or long-term functional impairment.

For current practice, the evidence supports a risk-stratified clinical framework rather than a fixed screening protocol. Younger asymptomatic children have a relatively low incidence and can reasonably remain under symptom-based clinical surveillance. Adolescents aged ≥10 years warrant more active questioning about pain, gait, weight bearing, and function and a lower threshold for MRI. Adolescents with additional risk modifiers or HSCT represent a logical population in whom targeted imaging deserves prospective evaluation. However, current evidence does not justify prescribing a universal baseline MRI, a fixed screening interval, or a specific imaging schedule outside protocolized care or research. This distinction is important: risk stratification is supported by the evidence, whereas a validated risk-based MRI algorithm does not yet exist.

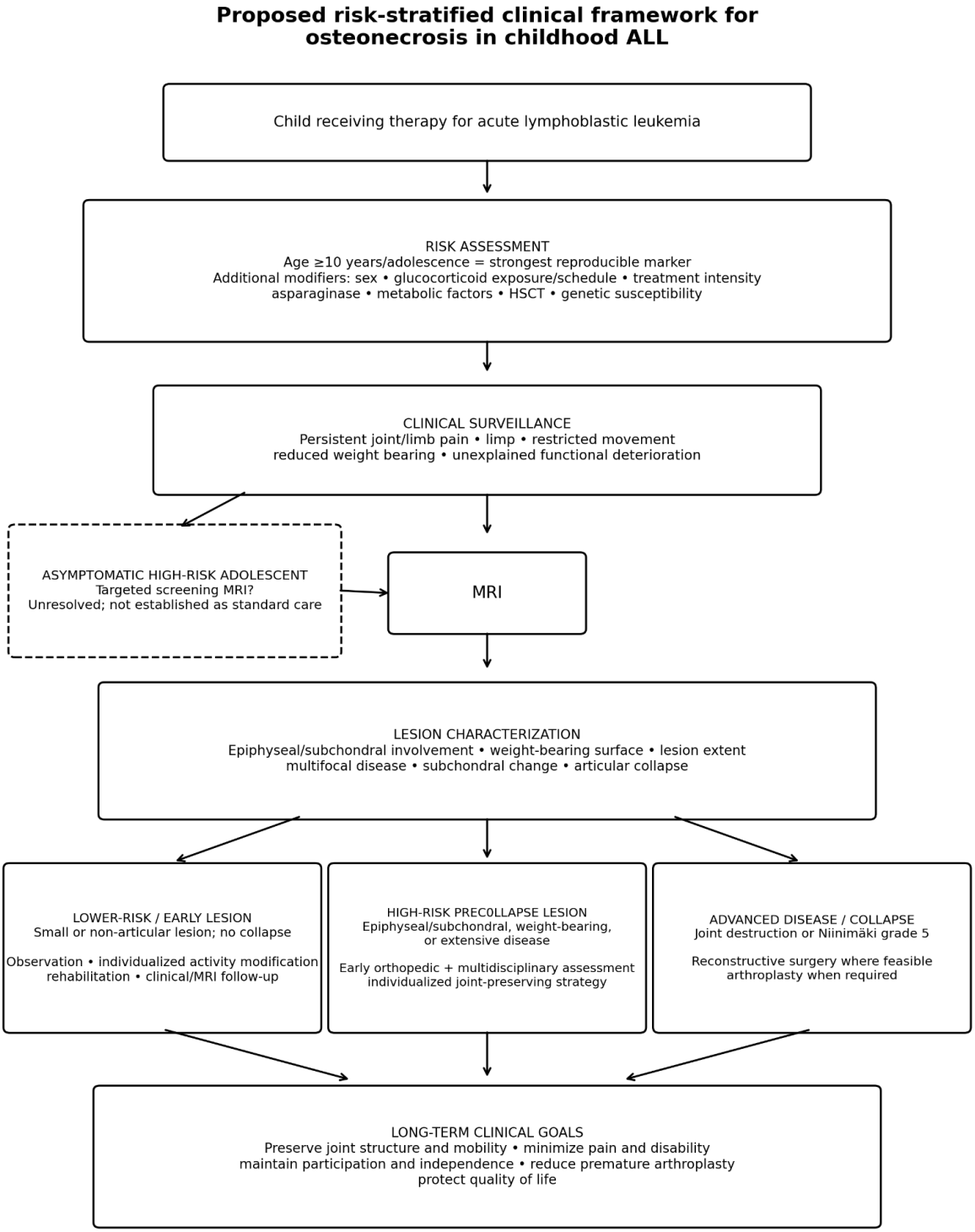
4.2. The MRI Screening Dilemma

MRI creates both the major opportunity and the major uncertainty in ALL-associated ON. It detects lesions before radiographic collapse and frequently before symptoms [4,11,12,17]. Earlier recognition could theoretically preserve the interval in which joint-preserving treatment remains possible. At the same time, serial-MRI studies demonstrate that many lesions remain stable or disappear without progression [8,10,22].

The value of screening therefore depends less on MRI sensitivity than on clinical actionability. Detecting an asymptomatic lesion is beneficial only if its risk of progression can be estimated with reasonable accuracy and if an intervention initiated at that stage improves an outcome that matters to the patient. Neither requirement has yet been adequately demonstrated. Universal screening consequently risks overdiagnosis and unnecessary restriction or treatment, whereas a purely symptom-triggered strategy risks identifying high-risk epiphyseal disease after structural damage has already occurred.

Targeted MRI in high-risk adolescents remains the most plausible intermediate strategy, but it should currently be regarded as a hypothesis to test rather than a standard to implement [11,12]. Future screening studies should prospectively define which MRI characteristics trigger observation, closer imaging, orthopedic referral, or intervention. Comparisons should

then determine whether this strategy reduces collapse, arthroplasty, chronic pain, and functional disability—not merely whether it detects more lesions. A proposed risk-stratified clinical framework integrating patient risk assessment, clinical surveillance, MRI-based lesion characterization, and stage-adapted management is presented in Figure 1.



Proposed evidence-synthesis framework; not a validated clinical guideline.

Figure 1. Proposed risk-stratified clinical framework for osteonecrosis in childhood ALL

The framework integrates patient risk assessment, clinical surveillance, MRI-based lesion characterization, and stage-adapted management. Targeted MRI screening of asymptomatic high-risk adolescents is presented as a potential strategy requiring prospective validation, rather than established standard care.

4.3. Balancing Osteonecrosis Prevention and Antileukemic Efficacy

The central problem in primary prevention is that glucocorticoids are simultaneously a major contributor to ON and an indispensable component of curative ALL therapy. The objective cannot therefore be simple exposure minimization.

Intermittent glucocorticoid scheduling provides the strongest proof that treatment design can reduce ON risk [16], but its effect depends on the surrounding regimen, including asparaginase exposure and overall treatment intensity [18]. The lack of a consistent difference between dexamethasone and prednisone across protocols further suggests that exposure pattern, pharmacokinetics, patient age, and multidrug context matter more than drug identity alone [7,17].

This distinction also separates primary prevention of ON occurrence from secondary prevention of progression after an early lesion has appeared. Primary prevention must preserve leukemia-control efficacy. Secondary prevention could potentially target a smaller subgroup with high-risk precollapse disease, thereby limiting intervention to patients most likely to benefit. At present, however, no metabolic, pharmacological, or imaging-guided strategy has been shown to reliably prevent progression while maintaining oncological safety [12,39,42].

A future individualized model could integrate age, treatment exposure, pharmacokinetics, metabolic phenotype, and validated genetic markers. Such an approach would be preferable to indiscriminate treatment reduction, but it remains investigational.

4.4. Current Evidence Gaps and Future Directions

The major imbalance in the literature is clear: risk factors and imaging are much better characterized than treatment effectiveness. Pediatric management studies remain dominated

by small observational cohorts, heterogeneous disease stages, inconsistent outcome definitions, and limited comparator groups [12,39-41]. Evidence derived from adult or non-oncologic ON cannot automatically be transferred to children receiving ALL therapy because skeletal maturity, healing capacity, treatment exposure, infection risk, and expected lifespan differ substantially.

This also argues against searching for a single treatment pathway applicable to every MRI lesion. A small extra-articular lesion that is stable on follow-up does not present the same clinical problem as an extensive precollapse femoral-head lesion in an adolescent. Future trials should therefore use lesion phenotype and structural risk to define eligibility. High-risk precollapse disease is the population in which joint-preserving strategies are most logically tested, while advanced collapse represents a fundamentally different therapeutic stage.

Standardized imaging definitions and classification remain essential [35-37]. Prospective multicenter studies should integrate lesion size and location with clinical, pharmacokinetic, metabolic, and pharmacogenomic factors to identify predictors of progression rather than predictors of ON alone. Intervention studies should then evaluate predefined stage-adapted strategies using meaningful comparator groups.

Outcome selection also requires improvement. Radiological stabilization is important but does not fully represent the burden of ON. Survivors with severe disease can experience persistent deficits in strength, flexibility, mobility, endurance, pain, and physical quality of life, with patients requiring hip surgery showing some of the greatest long-term impairment [13-15,38]. Future studies should therefore incorporate patient-reported outcomes, objective physical-performance measures, participation, need for arthroplasty or revision surgery, and long-term orthopedic and rehabilitation outcomes.

This synthesis is limited by substantial heterogeneity in treatment protocols, imaging schedules, ON definitions, anatomical sites, and outcome reporting. Symptom-detected and systematically MRI-detected ON represent different clinical phenotypes and should not be compared as if they were equivalent. Older landmark studies also remain necessary because contemporary randomized evidence, especially regarding management, is scarce.

5. Conclusions

Osteonecrosis is an important treatment-related complication of childhood ALL, with the

highest risk occurring in adolescents aged ≥10 years [5-7,16,30]. Glucocorticoid exposure is central to its development, but ON reflects interactions among treatment schedule and intensity, asparaginase, metabolic factors, skeletal maturation, and individual susceptibility [17-21]. Therefore, adolescents represent the group in whom clinical vigilance should be greatest.

MRI is the most sensitive method for detecting early, multifocal, and asymptomatic ON, but many lesions remain stable or resolve, whereas a smaller subset progresses to irreversible articular collapse [10-12]. The optimal balance between symptom-triggered, universal, and targeted high-risk MRI surveillance therefore remains uncertain.

Minimizing long-term functional morbidity requires a risk-adapted approach rather than a single standard pathway. Prevention should focus on optimizing glucocorticoid exposure without compromising antileukemic efficacy, while established ON should be managed according to symptoms, lesion location, structural severity, and risk of progression [4,12,16-18,39]. Early-stage disease may be observed with clinical and MRI follow-up and individualized rehabilitation, whereas high-risk precollapse lesions warrant early orthopedic assessment and consideration of joint-preserving strategies. Advanced collapse may ultimately require arthroplasty. Across all stages, multidisciplinary care involving oncology, radiology, orthopedics, and rehabilitation is essential [4,12,15,39]. Stronger prospective evidence is still needed to determine which early interventions best preserve joint structure, mobility, participation, and long-term quality of life [10,13-15,38,39].

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