

Osteonecrosis in Adults With Acute Lymphoblastic Leukemia: An Unmet Clinical Need

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Abstract

Osteonecrosis is a serious complication of antileukemic therapy associated with severe pain and reduced mobility, ultimately leading to joint destruction and significant long-term morbidity. The 5-year cumulative incidence of osteonecrosis ranges from 11% to 20% in adolescents and young adults to 3% to 8% in patients aged 30 years and older. Most symptomatic patients have multiple joints affected, which in turn poses a risk factor for developing severe osteonecrosis. Osteonecrosis has a multifactorial genesis. Treatment-associated risk factors for developing osteonecrosis depend on the therapeutic context including the use of glucocorticosteroids and the simultaneous and/or intensified use of asparaginase (ASP) which may, among others, exert its effect on blood supply to the bone through hypertriglyceridemia, hypercholesterolemia, and hypertension. Allogeneic hematopoietic stem cell transplantation, bloodstream infections, and genetic factors may additionally impact the risk of osteonecrosis. In this article, the authors used the best available evidence in the literature to develop management recommendations for the use in the context of steroid and asparaginase containing regimens. These considerations may be helpful for similar treatment approaches.

Current rates of acute lymphoblastic leukemia (ALL) in adults nowadays attain 50%-70% depending on age and risk group. With a higher proportion of survivors, increasing attention is paid to identification and prevention of acute and late adverse effects. Osteonecrosis is a serious complication of anti-leukemic therapy associated with severe pain and reduced mobility, ultimately leading to joint destruction and significant long-term morbidity. Pediatric study groups reported an alarming incidence of osteonecrosis in older children and adolescents treated for ALL. Treatment strategies for adult ALL are often based on similar backbones. Therefore, physicians treating adult ALL patients and the respective study groups need to be aware of the risk of osteonecrosis particularly in younger adults.

The pathogenesis of osteonecrosis in patients with ALL is still incompletely understood. Most likely it is caused by a temporary or permanent disruption of the blood supply to the bone by intra- and extraluminal obliteration of the nutrient artery, which is further aggravated by glucocorticoid-induced arteriopathy and direct adverse effects of the antileukemic drugs on bone

remodeling. Details on current concepts of the pathogenesis of osteonecrosis are reviewed elsewhere.¹ Briefly, microthrombi and lipid emboli/hyperlipidemia cause intraluminal obliteration. Lipocyte proliferation and lipid accumulation in osteoblasts and osteocytes cause (intramedullary) intraosseous compartment syndrome (extraluminal obliteration). Both mechanisms additionally trigger intravascular coagulation.

The Nordic Society of Paediatric Haematology and Oncology (NOPHO) reported symptomatic osteonecrosis in children and young adults, aged 1-45 years, treated according to the NOPHO ALL2008 protocol.² The 5-year cumulative incidence (CI) of osteonecrosis for adults (aged 19.0-45.0 y) was 15%. The Children's Oncology Group reported an incidence in patients aged 16-21 years of 19.9% in trial Children's Cancer Group (CCG)-1961 and of 18.0% in trial CCG-1882. These data consistently show nonsignificant differences of symptomatic osteonecrosis by age groups. The NOPHO study reported a CI of osteonecrosis in adolescents (10 to <19 y) of 20%. In UKALLXII/ECOG2993, the CI of symptomatic osteonecrosis in patients aged <20 years was 17% at 10 years compared to 11% (20-29 y), 3% (30-39 y), and 6% (≥40 y).³ On sequential Dana-Farber Cancer Institute (DFCI) ALL consortium protocols, osteonecrosis were significantly more likely to be diagnosed in patients aged <30 years (20%) compared to patients aged 30-50 years (8%).⁴ An overview of studies reporting on osteonecrosis in adults with ALL is given in Supplemental Digital Content, Table 1, <http://links.lww.com/HS/A138>. Of note, all these analyses were based on the Kaplan-Meier method and may therefore overestimate the incidence, whereas the Aalen-Johansen method might be more appropriate since it takes competing risks into account.

The median interval between ALL diagnosis and osteonecrosis diagnosis in adults is reported between 1.6 and 2.2 years and, thus, longer than in children and adolescents.²⁻⁴ Osteonecrosis, however, occurs as late as 7.7 years after ALL diagnosis.^{3,4} Leading symptoms at diagnosis are bone pain, decreased mobility in a joint, and limping.² Up to 71% of

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patients had multiple joints affected, mainly the hips, knees, and shoulders.^{2,3} In the NOPHO, United Kingdom National Acute Lymphoblastic Leukaemia (UKALL) study, and DFCI study, 61%-78% of patients with severe osteonecrosis underwent surgical interventions (eg, arthroplasty, joint replacement), more patients were planned for surgery.²⁻⁴ The majority of patients with severe osteonecrosis still experience symptoms years following osteonecrosis diagnosis.² In the NOPHO study, age and multiple joints affected are risk factors for developing severe osteonecrosis.² Controversy still exists on the association of osteonecrosis and event-free survival.

The most recognized risk factor for developing osteonecrosis in the context of ALL therapy is age.^{3,5,6} Some data suggest that adolescents and young adults (16-20 y) are at special risk.^{3,4,6,7} Although inconsistently reported, sex is considered as another important risk factor in adolescents with females <15 years and males ≥15 years being at highest risk for developing osteonecrosis.^{2,6,7} The NOPHO and DFCI study did not show any difference in CI of osteonecrosis between female and male adults.^{2,4} These data suggest that differences in puberty between female and male including sexual and growth hormone production, peak height velocity and peak bone mass accrual, bone maturation and ossification as well as changes in hemostaseology may contribute to osteonecrosis development.^{1,8} These factors are rather negligible in adults after the third decade of life. This is emphasized by the UKALLXII/ECOG2993 data showing a decline of osteonecrosis incidence in patients aged 30 years and older.³

The association of osteonecrosis with the use of glucocorticosteroids (GCs) is unquestioned. In most trials, the use of dexamethasone (compared to prednisolone) had no influence on osteonecrosis incidence.⁹⁻¹² In trial CCG-1961, alternate-week versus continuous dexamethasone scheduling during delayed intensification significantly reduced osteonecrosis incidence in pediatric patients with ALL.¹³ Of note, high-risk patients who developed osteonecrosis had a 17.6% better event-free survival than those who did not.

There is, however, increasing evidence that the simultaneous and/or intensified use of asparaginase (ASP) is associated with increased risk of osteonecrosis by indirect effects influencing GC pharmacokinetics (eg, low dexamethasone clearance) and aggravating/causing hyperlipidemia.¹⁴⁻¹⁶ The DFCI ALL consortium only recently reported an increased CI of osteonecrosis in patients treated on pegylated ASP based protocols compared to patients treated on earlier trials with native *Escherichia coli* ASP (CI 24% versus 5%, both with parallel application of steroids).⁴ Particularly, the parallel application of steroids and ASP and/or the application of steroids during ongoing activity of pegylated ASP may be associated with an increased risk. In the NOPHO study, prolonged exposure to hypertriglyceridemia or hypercholesterolemia was associated with increased risk of osteonecrosis.¹⁶ In St. Jude Total Therapy XV and XVI, ASP formulation (PEG-ASP more than native L-ASP) impacted hypertriglyceridemia.¹⁵ A recent analysis of the Dutch Childhood Oncology Group (DCOG) of 3 consecutive DCOG ALL protocols highlighted the relevance of therapeutic context on osteonecrosis development.¹⁷ In a controlled preclinical model, mice receiving ASP plus continuous dexamethasone experienced osteonecrosis more often than those receiving dexamethasone alone.¹⁸ Another preclinical study, however, showed that ASP added to a discontinuous dexamethasone regimen did not increase osteonecrosis occurrence in mice.¹⁹

A recent study combining clinical data and a preclinical murine model of osteonecrosis demonstrated that patients who developed hypertension during glucocorticoid containing phases of ALL therapy are at increased risk of developing symptomatic osteonecrosis and of more radiographically extensive epiphyseal osteonecrosis.²⁰ In the preclinical model, osteonecrosis occurrence and progression from arteriopathy to osteonecrosis were reduced by antihypertensive therapy.

Bloodstream infections were only recently identified as risk factor in the development of osteonecrosis and were associated with increased grade of osteonecrosis.²¹ Interestingly, most patients had only 1 recorded episode of bacteremia.

Allogeneic hematopoietic stem cell transplantation (HSCT) is widely performed in adults with ALL and may additionally impact the risk of osteonecrosis by graft-versus-host disease, exposure to calcineurin inhibitors, and cumulative dose of corticosteroids.^{22,23}

In a genome-wide association study in children with ALL, osteonecrosis was associated with inherited variations near glutamate receptor genes.²⁴ A subsequent study in children <10 years demonstrated enrichment of single nucleotide polymorphisms in mesenchymal stem cells, glutamate receptor, and adipogenesis pathways.²⁵ These data highlight that underlying mechanisms including genetic risk factors important for osteonecrosis development may differ across age groups. Data on genetic risk factors in adults are still missing.

Overall osteonecrosis has a multifactorial genesis (Figure 1), and so far, there are neither treatment nor pretreatment risk factors allowing identifying patients with high risk of osteonecrosis beforehand.

In the current trial of the German Multicenter Study Group for Adult ALL (GMALL) GMALL 08/2013, a pediatric-based regimen with intensive use of pegylated ASP is administered in patients aged between 18 and 55 years. Osteonecrosis is identified as an adverse event of special interest in the protocol and 80 participating sites are encouraged to report osteonecrosis on a timely basis. In the meantime, a number of reports of osteonecrosis have been received with a focus on younger adults aged between 18 and 35 years. While it is impossible to calculate the incidence of osteonecrosis during this ongoing trial, the study group decided to address the urgent clinical need of providing guidance for care. The authors used the best available evidence in the literature to develop management recommendations. These are primarily designed for the use in the context of the above-mentioned regimen, which contains repeated cycles of steroids alternating with applications of pegylated ASP at a dose range between 500 and 2000 U/m². Nevertheless, these considerations may be helpful for similar treatment approaches. We point to the fact that published data oftentimes were insufficient and recommendations hence were based on discussions with other experts and our expert knowledge. Here, we present our suggestions for clinical practice, which became part of a GMALL expert recommendation provided to all active sites. Consequently, the level of evidence (LoE) for most recommendations is mostly “authors recommendation,” that is, “GMALL recommendation” unless other evidence levels are specifically mentioned.

Diagnostic work-up

- Patients should be evaluated for symptoms of osteonecrosis (including pain, self-care activities of daily living, gait pattern) on a regular basis, for example, trimonthly, starting 6 months after ALL diagnosis until 5 years. Intervals should be adapted according to treatment schedule and follow-up appointments.
- Physicians in charge should be aware of osteonecrosis as a treatment-related complication in order to accelerate the diagnostic process at the onset of first symptoms.
- In symptomatic patients, osteonecrosis should be investigated by MRI. As severe osteonecrosis most commonly occurs in multiple locations including the weight-bearing joints, we recommend MRI including the symptomatic region as well as at least hips, knees, and shoulders.

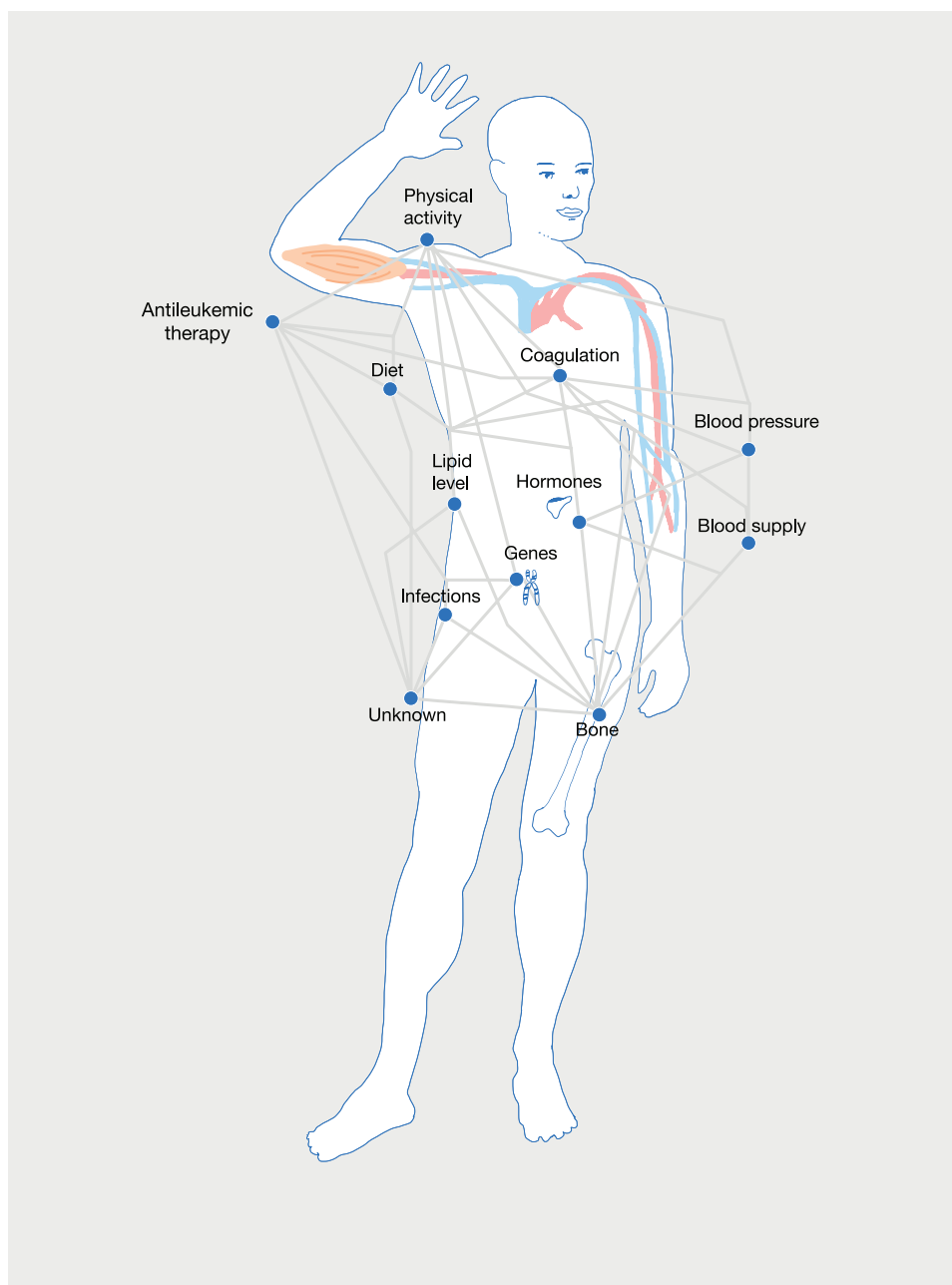


Figure 1. Scheme on the multifactorial genesis of osteonecrosis in the context of antileukemic therapy. Endogenous and exogenous factors both interact with and are influenced by each other leading among others to complex changes of hemostasis, lipid and hormone levels, blood pressure and supply, and physical activity. On the slightest modification of one of these factors, other risk factors change as well.

- Osteonecrosis should be classified according to the clinical classification systems Common Terminology Criteria for Adverse Events (<https://ctep.cancer.gov>) and Ponte Di Legno toxicity working group²⁶ as well as to the radiologic classification system developed by Niinimäki et al²⁷ to ensure comparability between trials. Radiological reports should provide information on the extent of articular surface involvement of each affected joint. As required, joint specific classification systems can be used additionally.
- In case of persisting joint/bone pain following acute or prior bloodstream infections without persisting inflammatory markers, affected areas/joints should be investigated by MRI to exclude superinfected osteonecrosis.
- Prospective MRI screening to capture asymptomatic patients developing osteonecrosis should be limited to clinical trials, as evidence-based interventions are not available yet.

Prophylaxis proposals

- In future trials with dexamethasone use during delayed intensification, alternate week scheduling may be considered (LoE: randomized trial in children¹³).
- During ASP treatment and activity, triglyceride and cholesterol levels should be measured 2-3 times per week. In case of prolonged hypertriglyceridemia and/or hypercholesterolemia, dietary measures should be initiated (LoE: authors recommendation, preclinical data available²⁸). Fibrates lower triglycerides but can so far not be recommended as clinical data on safety (including potential toxicities) and efficacy are still lacking.^{28,29} Omega-3-fatty acids were successfully used to reduce treatment-related hypertriglyceridemia in children with ALL and may be evaluated.³⁰

- Thrombosis prophylaxis with low-molecular-weight (LMW) heparin should be considered according to local standards, particularly during times of ASP activity. It should not go unmentioned that LMW heparin positively affects intravascular clotting and prevents progression of osteonecrosis in patients with a (primary) prothrombotic underlying disease.^{31,32} Whether the prevention of thrombosis during ASP-induced coagulation disturbance has an impact on the risk of osteonecrosis remains open.
- During glucocorticoid treatment, blood pressure should be monitored closely. Antihypertensive treatment should be initiated if indicated (LoE: authors recommendation, pre-clinical data available²⁰).
- The use of GCs in supportive care, for example, as anti-emetic, should be restricted, particularly during times of ASP activity (LoE: authors recommendation).

Management of osteonecrosis in adults with ALL is challenging and evidence-based guidelines are still lacking. A comprehensive overview on therapeutic approaches in children and adolescents is given elsewhere.³³ A brief summary of treatment options is given in Table 1. The lack of consensus on management of osteonecrosis in adults with ALL, however, requires individualized decisions considering localization of osteonecrosis and severity. Moreover, timing of osteonecrosis is crucial for continuation of ALL therapy and osteonecrosis-directed therapeutic interventions. To date, recommendations to adapt leukemia therapy cannot be given. Instead, considering the overall inconclusive association of drugs used in the treatment of adults with ALL and the development of osteonecrosis, we advise against modification of standard GMALL therapy as this may be associated with increased relapse risk. The protocol, however, allows individual adaptations of ASP therapy based on ASP activity and toxicity as published previously.³⁴

Additional information: fractures—a further important bone morbidity

Bone health including adequate bone mass in general is crucial for prevention of fractures, pain, loss of mobility, and

deformity, and thus adverse consequences on quality of life. The Canadian Steroid-Associated Osteoporosis in the Pediatric Population study in children demonstrated a high fracture rate in children with ALL at diagnosis and during chemotherapy.³⁵ Studies exploring bone health, including osteomalacia, osteopenia, and osteoporosis, in adults with ALL were missing so far. Only recently, the DFCI ALL consortium reported a CI of fractures in adolescent and young adult patients with ALL of 12%.⁴ Data from the DCOG-ALL9 study showed an aggravated bone density decline in children with symptomatic osteonecrosis, which may create a vicious circle leading to further worsening of osteonecrosis.³⁶ We therefore highly recommend assessing bone health in adults in its entirety.

Bone health assessment and prophylaxis

- Measurement of calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and 25-hydroxy vitamin D at ALL diagnosis and every 6 months subsequently. If necessary, supplementation of calcium and vitamin D to prevent osteomalacia and rickets is recommended (LoE: 2) Of note, osteopenia and osteoporosis cannot be prevented by giving vitamin D.
- Assessment of hypogonadism and other endocrinopathies on a regular basis, if necessary replacement (LoE: 2).
- Promotion of physical activity and exercise to enhance muscle force and bone accrual within the limits of illness (LoE: 2).
- Consider bone densitometry according to the International Society for Clinical Densitometry (ISCD) guidance at start and end of maintenance, particularly in patients <35 years. In patients with back pain at any time, lateral spine radiographs or MRI should be conducted to check for vertebral fractures.
- Treatment of fractures including bisphosphonate therapy should be discussed with the endocrine team and follow the ISCD guidance.

In conclusion, young adults with ALL are at increased risk for developing severe osteonecrosis. Collaborative, interdisciplinary efforts and prospective studies are necessary to determine the true scale of symptomatic osteonecrosis, the risk factors, and radiological features that predict for progression and the development of symptomatic osteonecrosis in adults treated for ALL. Stratified interventions specifically targeting patients at high risk of developing osteonecrosis are urgently needed. To this end, as a first step, we initiated a prospective standardized capturing of adults with ALL developing osteonecrosis within the GMALL study and we will document the interventions and outcomes in detail.

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Table 1

Brief Summary of (Prophylactic) Treatment Options for Osteonecrosis.

Interventions	Suggestions
Pain management	Effective pain management is crucial
Physical therapy	Use of crutches is controversially discussed but is a regular part of care in other osteonecrosis conditions. Osteonecrosis in the upper limbs should be excluded by MRI before use Physical therapy is recommended
Pharmacologic interventions	Low-molecular-weight heparin Prostacyclin analogs Statins Bisphosphonates
Surgical interventions	Core decompression Reduction of intraosseous pressure Promotion of healing processes Prn combined with autologous or mesenchymal stem cells Arthroplasty Surface replacement Osteotomy Total joint replacement
Others	Antihypertensive treatment Treatment of prolonged hypertriglyceridemia/hypercholesterolemia, eg, dietary measure, omega3-fatty acids

Of note, the options are covered in the literature but lack sufficient quality evidence.
Prn = pro re nata.

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