

# Management and treatment of osteonecrosis in children and adolescents with acute lymphoblastic leukemia

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The online version of this article has a Supplementay Appendix.

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**Supplemental data, Table 1. Search strategy**

MeSH headings and text words that have been used to search in PubMed/ Medline:

#1 osteonecrosis	osteonecrosis OR avascular necrosis of bone OR aseptic necrosis of bone OR avascular necrosis OR aseptic necrosis OR bone necrosis OR ischemic necrosis of bone OR femoral head necrosis OR bone infarction
#2 children	infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR perinat* OR postnat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR school age* OR infancy OR schools, nursery OR infant, newborn
#3 childhood cancer	leukemia OR leukaemia OR leukemi* OR leukaemi* OR acute lymphoblastic leukemia OR acute lymphocytic leukemia OR acute lymphoid leukemia OR ALL OR precursor cell lymphoblastic leukemia-lymphoma OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR leukemia lymphocytic acute OR leukemia, lymphocytic, acute[mh]
#4 surgery	surgery AND arthroplasty OR joint arthroplasty OR total joint arthroplasty OR joint replacement OR total joint replacement OR replacement arthroplasty OR joint prosthesis OR cemented total joint arthroplasty OR hybrid total joint arthroplasty OR resurfacing arthroplasty OR hemi-resurfacing arthroplasty OR hemiarthroplasty OR hip arthroplasty OR total hip arthroplasty OR THA OR hip replacement OR hip replacement arthroplasty OR total hip OR hip prosthesis OR knee arthroplasty OR total knee arthroplasty OR knee replacement OR knee replacement arthroplasty OR total knee OR knee prosthesis OR ankle arthroplasty OR ankle replacement arthroplasty OR ankle prosthesis OR core decompression OR osteotomy OR bone grafting OR bone transplantation OR vascularized fibular graft OR arthrodesis OR autologous bone marrow injection OR bone marrow grafting OR bone marrow transplantation

#5 biphosphonates	bisphosphonates OR bisphosphonate* OR diphosphonates OR diphosphonate* OR alendronate OR alendronic OR 4-Amino-1-Hydroxybutylidene 1,1-Biphosphonate OR aminohydroxybutane bisphosphonate OR MK217 OR MK-217 OR MK 217 OR Fosamax OR alendronate sodium OR pamidronate OR 1-hydroxy-3-aminopropane-1,1-diphosphonic acid OR APD OR amidronate OR pamidronate monosodium OR pamidronate disodium OR dimethyl-pamidronate OR pamidronate OR pamidronic OR AHPPrBP OR aminopropanehydroxydiphosphonate OR aminohydroxypropylidene diphosphonate OR Aredia OR etidronic acid OR etidronate OR etidronic OR didronel OR hydroxyethylidene diphosphonic OR HEDP OR EHDP OR HEDSPA OR clodronic acid OR clodronate OR clodronic OR Bonafos OR risedronate OR risedronic OR Actonel OR tiludronate OR tiludronic OR skelid OR olpadronate OR olpadronic acid OR Me2-APD OR Me2APD OR Me2 APD OR incadronate OR zoledronate OR zoledronic OR zometa OR risedronate OR Bonafos OR Bonephos OR ibandronate OR ibandronic OR BM 21.0955 OR BM 210955 OR BM-210955 OR BM210955 OR BM-21.0955 OR Cl2SMBP OR CGP 42446 OR CGP-42446 OR Neridronate	
#6 hydroxymethylglutaryl CoA reductase inhibitors	hydroxymethylglutaryl CoA Reductase Inhibitors OR HMG CoA reductase inhibitors OR HMG-CoA reductase inhibitors OR hydroxymethylglutaryl Coenzyme A inhibitors OR statins OR HMG-CoA statins OR statin* OR lovastatin* OR mevacor OR mevinolin OR pravastatin* OR pravachol OR lipostat OR simvastatin* OR zocor OR fluvastatin* OR lescol OR fluindostatin OR atorvastatin* OR lipitor OR rosuvastatin* OR cerivastatin* OR baycol OR atorvastatin* OR meglutol OR pitavastatin	
#7 anticoagulants	anticoagulants OR anticoagulant drugs OR anticoagulant agents OR Anticoagulant* OR indirect thrombin inhibitors OR antithrombins OR fibrinolytic agents OR heparin OR low-molecular-weight heparin OR coumarins OR vitamin K inhibitor OR vitamin K antagonist	
#8 hyperbaric oxygen	hyperbaric oxygenations OR hyperbaric oxygen therapy OR oxygen inhalation therapy	
Different searches were combined	#1 AND #3 #1 AND #2 AND #4 #1 AND #3 AND #4 #1 AND #2 AND #5 #1 AND #3 AND #5 #1 AND #2 AND #6	#1 AND #3 AND #6 #1 AND #2 AND #7 #1 AND #3 AND #7 #1 AND #2 AND #8 #1 AND #3 AND #8

**Supplemental data, Table 2A. Checklist for methodological appraisal of included studies**

Adapted from the Oxford Centre for Evidence-based Medicine (OCEBM, "The Oxford 2011 Levels of Evidence")

Level	Study design
1	Randomized-controlled trials
2	Prospective (non-randomized) case-control studies; Prospective (non-randomized) cohort studies
3	Retrospective case-control studies; Retrospective cohort studies; Prospective case series, ≥10 patients
4	Retrospective case series, ≥10 patients; Prospective case series, <10 patients
5	Single case reports; Retrospective case series, <10 patients; consensus report or guideline

**Supplemental data, Table 2B. Checklist for Recommendation**

Amount of evidence	Interpretation
1 or more level 1 studies	Consistent high-quality evidence
consistent level 2 or 3 studies	Moderate evidence
level 4 studies	Low-quality evidence
level 5 evidence <i>or</i> troublingly inconsistent or inconclusive studies of any level	

**Supplemental data, Table 3. Evidence table for prevention, and intervention studies**

	LEVEL OF EVIDENCE				
	1	2	3	4	5
<b>NON-SURGICAL INTERVENTIONS</b>					
Bisphosphonates		Kotecha 2010 <sup>(19)</sup> *		Nguyen 2006 <sup>(23)</sup> *, Leblicq 2013 <sup>(26)</sup> *, Padhye 2013 <sup>(27)</sup> *	Greggio 2010 <sup>(17)</sup> *
Hyperbaric oxygen			Bernbeck 2004 <sup>(20)</sup> *		
Prostacyclin analog				Jäger 2009 <sup>(24)</sup> *	
Chemotherapy adjustments after occurrence of osteonecrosis	NA				
<b>SURGICAL INTERVENTIONS</b>					
Implantation of autologous osteogenic cells				Wells 2009 <sup>(22)</sup> *	Clar 2010 <sup>(16)</sup> *, Muller 2008 <sup>(18)</sup> *
Osteochondrol grafting				Gortz 2010 <sup>(21)</sup> *	Inoue 2012 <sup>(28)</sup> *
Resurfacing arthroplasty				Karimova 2008 <sup>(25)</sup> *	
Osteotomy					Sabharwal 2012 <sup>(29)</sup> *
<b>PREVENTIVE STRATEGIES</b>					
Prednisone instead of dexamethasone					
Overall	Mitchel 2005 <sup>(74)</sup> †		Straus 2001 <sup>(4)</sup> †		Moricke 2008 <sup>(75)</sup> †
<10 years of age	Bostrom 2003 <sup>(73)</sup> †, Igarashi 2005 <sup>(76)</sup> †				Mattano 2008 <sup>(72)</sup> †
≥10 years of age	Vrooman 2013 <sup>(71)</sup> *				Mattano 2008 <sup>(72)</sup> *
Discontinuous corticosteroid pulses					
Overall	NA				
<10 years of age	NA				

Abbreviations: NA, not available. Red, low-quality or no evidence; Orange, moderate evidence; Green, consistent high-quality evidence. \*, recommended/beneficial; †, not recommended/ not beneficial.

**Supplemental data, Table 4A. Overview of non-surgical interventions studies in pediatric patients with acute lymphoblastic leukemia**

INTERVENTIONS	NO. OF PEDIATRIC ALL PATIENTS	FOLLOW-UP (MEAN (RANGE) MONTHS)	OUTCOME	
			CLINICAL	RADIOLOGICAL
<b>NON-SURGICAL INTERVENTIONS (SEE TABLE 5 FOR AN EXTENSIVE DESCRIPTION ON OUTCOME)</b>				
<b>BISPHOSPHONATES</b>				
<i>Kotecha 2010<sup>(19)</sup></i>	3 A <sup>®</sup> 3 A <sup>®</sup> &P <sup>®</sup> 3 P <sup>®</sup> 8 controls	17 (7-29) 22(13-31) 22 (18-24)	+ (pain, function, ROM, HHS <sup>#</sup> )	- / ~
Nguyen 2006 <sup>(23)</sup>	6 P <sup>®</sup>	-5/6 pt.: 24 -1/6 pt.: 12 ( TJR)	+ (pain, function, ROM, HHS <sup>#</sup> )	- / ~
Greggio 2010 <sup>(17)</sup>	1 A <sup>®</sup>	78	+ (pain, function, ROM, HHS <sup>#</sup> )	- / ~
Leblicq 2013 <sup>(26)</sup>	14 P <sup>®</sup> 3 controls	23.5 (6-72)	+ (pain, function)	+ / - / ~
Padhye 2013 <sup>(27)</sup>	12 Z <sup>®</sup>	11.2 (5.4-18.5)	+ (pain)	- / ~
<b>HYPERBARIC OXYGEN</b>				
Bembeck 2004 <sup>(20)</sup>	21	NA	+ (pain)	~
<b>PROSTACYCLIN ANALOG</b>				
Jäger 2009 <sup>(24)</sup>	7	20,8 (6-53)	+ (pain, function, HHS <sup>#</sup> )	Early stage: + Late stage: -

Abbreviations: A<sup>®</sup>, Alendronate; P<sup>®</sup>, Pamidronate; Z<sup>®</sup>, Zoledronate; NA, not available; ROM, range of motion; HHS, Harris hip score; +, positive effect on outcome; -, outcome measure worsened; ~, stable/ unchanged outcome. \*, median FU time reported instead of the mean FU time; #, The Harris hip score(2) covers pain, function and mobility of the joint.

**Supplemental table, Table 4B. Overview of surgical interventions studies in pediatric patients with acute lymphoblastic leukemia**

INTERVENTIONS	NO. OF PEDIATRIC ALL PATIENTS	FOLLOW-UP (MEAN (RANGE) MONTHS)	OUTCOME	
			CLINICAL	RADIOLOGICAL
<b>SURGICAL INTERVENTIONS</b>				
<b>IMPLANTATION OF AUTOLOGOUS OSTEOGENIC CELLS</b>				
Clar 2010 <sup>(16)</sup>	1	66	Improvement of function in 4/7 pt., reduction of pain in 3/6 pt. -Unlimited daily activities <sup>[6]</sup>	
Muller 2008 <sup>(18)</sup>	1	NA	-Pain reduced/ daily activity improved	
Wells 2009 <sup>(22)</sup>	5	28 (18-49)	-3/5 pt. (5 hips) increased pain/ deteriorated function, 1/5 pt. intermittent pain/ some limitation of function, 1/5 pt. no pain/ improved function	3/5 pt. (5 hips) collapsed
<b>OSTEOCHONDROL GRAFTING</b>				
Gortz 2010 <sup>(21)</sup>	5	52 (27-96)	4/5 pt. favorable outcome for d' Aubigné and Postel <sup>#</sup> , 0/5 ALL pt. needed TJR 1/5 needed osteotomy and graft revision	All pt. showed graft healing within 1 year, 1/5 collapsed (FU 45 mo.)
Inoue 2012 <sup>(28)</sup>	1	73	Function, ROM improved, no pain	X-ray: slight deformity of humeral head, MRI: no progression
<b>RESURFACING ARTHROPLASTY</b>				
Karimova 2008 <sup>(25)</sup>	7	31.8 (11-60)	5/7 pt. needed TJR of 7 hips (3 loosening, 4 pain)	Revision-free survival negatively associated with lesion size (volume % of femoral head): - Lesion size of revised hips: 70.4 (43.2-95.6)% - Lesion size of non-revised hips: 31.0 (21.0-39.3)%
<b>OSTEOTOMY</b>				
Sabharwal 2012 <sup>(29)</sup>	1	36	Pain reduced, HHS <sup>#</sup> improved	X-ray: less leg-length discrepancy

Abbreviations: TJR, total joint replacement; NA, not available; #, the Harris hip score (HHS) and the d' Aubigné and Postel score(3) cover pain, function and mobility of the joint.

**Supplemental table, Table 5. Results of non-surgical interventions in pediatric patients with acute lymphoblastic leukemia**

	BISPHOSPHONATES	HYPERBARIC OXYGEN THERAPY	PROSTACYCLIN ANALOG
References	Kotecha 2010 <sup>(19)</sup> , Nguyen 2006 <sup>(23)</sup> , Greggio 2010 <sup>(17)</sup> , Leblcq 2013 <sup>(26)</sup> , Padhye 2013 <sup>(27)</sup>	Bembeck 2004 <sup>(20)</sup>	Jäger 2009 <sup>(24)</sup>
Number of studies	5	1	1
<b>CLINICAL OUTCOME</b>			
Pain (VAS/ analgesics)	-pain reduced/ absent: 3/3 P <sup>®</sup> vs. 3/6 A <sup>®</sup> vs. 1/8 controls reduction of analgesics: 3/3 P <sup>®</sup> vs. 3/6 A <sup>®</sup> (after adding P <sup>®</sup> : 2/3) vs. 2/8 controls <sup>[19]</sup> -after 1 year P <sup>®</sup> : 4/6 improved, 2/6 deteriorated (those continuing dexamethasone); after 2 years P <sup>®</sup> : 3/6 worsened, 3/6 unchanged <sup>[23]</sup> - A <sup>®</sup> : 2/2 pain free <sup>[17]</sup> - P <sup>®</sup> : 4/14 pain stable, 10/14 pain reduced/ absent vs. controls: 3/3 pain stable <sup>[26]</sup> - Z <sup>®</sup> : 4/12 pain free, 7/12 persistent mild/ moderate pain not limiting activities, 1/12 pain restricting activities <sup>[27]</sup>	5/11 patients pain free after 15 treatments, all patients pain free after 40 treatments	pain score reduced within 1 week and sustained afterwards
Function (limp, walking time)	-improvement of function: 3/3 P <sup>®</sup> vs. 2/6 A <sup>®</sup> (after adding P <sup>®</sup> : 3/4) vs. 1/8 controls <sup>[19]</sup> - P <sup>®</sup> : 4/6 requiring crutches/ walking stick, able to maintain standing balance, 1/6 with weight-bearing restriction for long distance, and 1/6 with no weight-bearing restrictions/ limp <sup>[23]</sup> - A <sup>®</sup> : 2/2 recovery of function (capable of mild sport activities) <sup>[17]</sup> - P <sup>®</sup> : 6/14 stable, 8/14 improvement vs. controls: 1/3 stable, 2/3 improvement <sup>[26]</sup>	NA	function improved within 3 months and sustained afterwards
Range of motion (abduction, rotation, adduction)	-improvement of ROM: 3/3 P <sup>®</sup> vs. 2/6 A <sup>®</sup> (after adding P <sup>®</sup> : 3/4) vs. 1/8 controls <sup>[19]</sup> - P <sup>®</sup> : 4/6 grossly restricted ROM, 1/6 mild restricted ROM, 1/6 no restricted ROM <sup>[23]</sup>	NA	NA
Harris hip score # (pain, function, mobility)	NA	NA	improvement of HHS within 3 months and sustained afterwards
Need for/ time until surgery	- 1/6 needed TJR within 2 years after start P <sup>®</sup> , 2/6 needed TJR shortly thereafter <sup>[23]</sup> - 1/12 advised to undergo joint replacement surgery <sup>[27]</sup>	No effect on the need for surgery: -5/19 HBO group vs. 2/8 non-HBO group	2/8 patients needed additional surgery 1 core decompression after 10 months 1 cancellous bone transplantation after 30 months
<b>RADIOLOGICAL OUTCOME</b>			
Radiological staging (e.g. Ficat & Arlet/ ARCO/ Stulberg)	- P <sup>®</sup> : 2/6 stable (stage III), 4/6 collapsed (stage V) within 2 years <sup>[23]</sup> - P <sup>®</sup> : 6/14 improvement, 3/14 stable, 5/14 progression vs. controls: 1/3 improvement, 2/3 NA <sup>[26]</sup> - Z <sup>®</sup> : 5/12 stable, 7/12 progression (ARCO stages) <sup>[27]</sup>	NA	improvement of ARCO stages only in early stages (I, II) progression of ARCO stage in 3 patients with stage III
Collapse	- P <sup>®</sup> : not avoiding collapse. 1 <sup>st</sup> year more favorable than 2 <sup>nd</sup> year <sup>[23]</sup>	NA	NA
Size of lesions	-no difference in volume between bisphosphonate users and controls; numbers too small to validate a difference between P <sup>®</sup> and A <sup>®</sup> <sup>[19]</sup>	NA	NA
Number of localisations	NA	No clear reduction in number of lesions; only a trend towards conversion of osteonecrosis to bone marrow edema for those <10 years	NA
Shape of the joint	A <sup>®</sup> : remodeling of femoral head, minimal flattening (FU 30 months) <sup>[17]</sup>	NA	NA

Abbreviations: VAS, visual analog scale; A<sup>®</sup>, Alendronate; P<sup>®</sup>, Pamidronate; Z<sup>®</sup>, Zoledronate; HHS, Harris hip score; ROM, range of motion; ARCO, Association of Research Circulation Osseous; TJR, total joint replacement; HBO, hyperbaric oxygen; FU, follow-up; NA, not available. #, The Harris hip score represent pain, function and mobility, a score of <70 was defined as a poor outcome (max. score 100).



## **Legends to figures**

**Supplemental data, Figure 1:** Flowchart of study identification and selection

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