

Title page

Title: The Italian Consensus Conference on the role of rehabilitation for children and adolescents with leukemia, central nervous system tumors, and bone cancer, part 2: treatment of motor function impairments.

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Abbreviations	
AIEOP	Italian Association of Pediatric Hematology and Oncology
CC	Consensus Conference
CIPN	Chemotherapy-induced neuropathy
CMS	Cerebellar mutism syndrome
CNS	Central nervous system
SIOP Europe	European Society of Oncological Pediatrics
HCPs	Health care professionals
HSCT	Hematopoietic stem cell transplantation
ICF-CY	International Classification of Functioning, Disability and Health for Children and Youth
IARC	International Agency for Research on Cancer
WHO	World Health Organization
MSTS	Musculoskeletal Tumor Society score
ROM	Range of movement
TNPEE	Neuro-psychomotor therapist of the developmental age

67 **Abstract:**

68 In Italy, 1400 children and 800 adolescents are diagnosed with cancer every year. About 80% of them
69 can be cured but are at high risk of experiencing severe side effects, many of which respond to
70 rehabilitation treatment. Due to the paucity of literature on this topic, the Italian Association of
71 Pediatric Hematology and Oncology organized a Consensus Conference on the role of rehabilitation
72 of motor impairments in children/adolescents affected by leukemia, central nervous system tumors,
73 and bone cancer to state recommendations to improve clinical practice. This paper includes the results
74 on the rehabilitation treatment.

75

76 **Introduction:**

77 Based on the data collected by the International Agency for Research on Cancer (IARC) from cancer
78 registries around the world, each year an estimated 215 000 cancers are diagnosed in children under
79 age 15 and about 85 000 cancers in those aged 15–19 years.¹ In Italy, around 1400 children and 800
80 adolescents are diagnosed with cancer every year.² In high-income countries, 80% of pediatric
81 patients can be cured, while in low-resource settings, survival rates are only about a quarter of those
82 in high-resource settings.¹ Children and adolescents diagnosed with cancer are at high risk of
83 experiencing severe side effects from cancer treatment, many of which respond to rehabilitation.
84 These side effects can negatively impact a child's quality of life and participation in daily activities
85 (e.g., play and attending school).³ Cancer and cancer treatments can negatively impact the major body
86 systems, including the musculoskeletal, cardiorespiratory, and neurological systems.⁴ The Italian
87 Association of Pediatric Hematology and Oncology (AIEOP) promoted the Italian Consensus
88 Conference (CC) on the role of rehabilitation for children and adolescents with leukemia, central
89 nervous system (CNS) tumors, and bone cancer to answer some questions on motor function
90 rehabilitation assessment and treatment. The main goal of this CC was to define the role of the
91 rehabilitation team and of the physiotherapist in the assessment (part 1) ⁵ and treatment (part 2) of
92 sensorimotor, neuro, and psychomotor impairments in children/adolescents affected by leukemia,

CNS tumors, and bone cancer. This paper includes the results on the rehabilitation treatment process, which aims to help children and adolescents manage the musculoskeletal, neurological, and psychomotor effects resulting from cancer and cancer treatments so as to restore and optimize function, mobility, and quality of life.

Methods

The European Society of Oncological Pediatrics (SIOP Europe) promoted the implementation of health care professional (HCPs) networks to support care activities, research, and training to create innovative, high-quality models of care.⁶ The high variability in rehabilitation approaches to pediatric cancer patients resulting from the lack of high-quality evidence⁷ led the AIEOP Rehabilitation Working Group to organize a CC with the aim to define the role of the rehabilitation team and to provide practice recommendations for the care of children/adolescents affected by leukemia, CNS neoplasms, and bone cancer. A systematic approach based on the Italian National System for Guidelines was followed.⁸ Detailed information on the composition of CC working groups (lead committee, technical scientific committee, panel of experts, multidisciplinary jury, and writing committee) as well as on the identification of questions, critical appraisal of the evidence, and recommendations development are available in the previous paper.⁵ Literature review strategies for the rehabilitation treatment of pediatric patients affected by cancer are reported in Supplemental Table 1. In both papers, the term “physiotherapist” refers to the physiotherapist and to the neuro-psychomotor therapist of the developmental age (TNPEE)⁹, two professionals who in Italy work with other specialists (occupational therapist, speech therapist, orthoptist) for the rehabilitation of patients in developmental age. In this CC, the term “rehabilitation” refers to the sensorimotor, neuro-, and psychomotor fields.

Results and recommendations:

118 For the role of HCPs in rehabilitation treatment, the CC produced seven general recommendations
119 (Table 1) and sixteen statements (Table 2), three for children/adolescents affected by all cancer types
120 and thirteen specific statements for the three subpopulations.

121

122 Question 1: “What are the rehabilitation goals for subjects in developmental age affected by cancer?
123 When should rehabilitation be done?”

124 Recommendations:

125 • "Rehabilitation should aim to prevent and/ or to improve the complications of sensorimotor,
126 cognitive, and psychosocial function during and after anticancer treatments.”

127 • "When indicated, rehabilitation should start as early as possible."

128 Statements are reported in Table 2.

129

130 Description:

131 Rehabilitation goals should be defined according to the biopsychosocial model of the World Health
132 Organization (WHO) International Classification of Functioning, Disability and Health for Children
133 and Youth (ICF-CY),²⁴ including Body Function and Structure, Activity, Participation,
134 Environmental Factors, and Personal Factors. This model emphasizes the need to support individuals
135 to achieve optimal capacity and participation in all aspects of life.²⁵ Multidisciplinary rehabilitation
136 can utilize the ICF-Childhood cancer model, an adapted ICF model, which encompasses the interplay
137 of childhood cancer and function to assist in defining rehabilitation goals and interventions.²⁶

138 Rehabilitation interventions for infants and young children diagnosed with cancer should aim to
139 support their neuro-psychomotor development, which could be delayed due to limitations determined
140 by the cancer itself and by cancer treatments.

141 **Leukemia**

142 Sharing preventive counselling indications during and after anticancer treatment with
143 children/adolescents affected by leukemia and their families may be useful. These subjects may need

144 to start a rehabilitation intervention at any moment of their cancer treatment due to the onset of
145 specific issues. “Early rehabilitation” is now a widely accepted concept; in the oncological setting, it
146 has been demonstrated that functional recovery is better in patients who start rehabilitation as soon
147 as possible.²⁷⁻³¹ There are several studies that evaluated the impact of various exercise programs on
148 different physical and psychosocial variables in children/adolescents affected by leukemia. These
149 studies were performed immediately after diagnosis, during intensive treatments,³²⁻³⁶ and up to their
150 completion, including subjects in the maintenance phase^{27,37-46} and survivors.⁴⁷⁻⁴⁹ A Cochrane
151 Systematic Review examined the effects of physical exercise interventions in children and
152 adolescents with acute lymphoblastic leukemia, with the preliminary findings supporting the benefits
153 of exercise for outcomes related to body composition, flexibility, and cardiorespiratory fitness.⁶
154 During the maintenance phase, if necessary, the rehabilitation treatment can be performed in the
155 community setting; adapted physical activity programs and/or the resumption of a sports activity
156 under the supervision of an exercise physiologist should be proposed.

157 **CNS tumors**

158 In children/adolescents affected by CNS tumors, early intensive rehabilitation is recommended.
159 Various studies have shown that in the acute rehabilitation phase these patients make comparable
160 functional gains, as do patients with stroke.⁵⁰ The multidisciplinary rehabilitation plan should be
161 integrated into the oncology setting to complement the intensive cancer treatment,²⁶ should continue
162 even after discharge from the hospital, and, if necessary, should be carried out repeatedly for long
163 periods.^{29,31,51,52}

164 **Bone cancer**

165 In children/adolescents affected by bone cancer, inpatient rehabilitation treatment is feasible, safe,
166 and well tolerated, as shown by the high rate of adherence reported in several studies.^{6,21,46,53} In the
167 first year after surgery, progressive improvement in all the physical outcomes in this population has
168 been registered, even when rehabilitation was performed during chemotherapy.²³ After the first year,
169 rehabilitation can also be combined with physical activity supervised by an exercise physiologist.^{19,22}

170

171 Question 2: "What characteristics should the individualized rehabilitation plan have?"

172 Recommendations:

- 173 • "The rehabilitation plan should be put in place by the multiprofessional team and personalized
174 according to the patient's goals."
- 175 • "The rehabilitation plan (modality, setting, intensity, and duration) should be tailored to the
176 subject's characteristics, clinical status, sensorimotor impairment, and treatment phase."
- 177 • "Any ongoing changes to the individualized rehabilitation plan should be made according to
178 the patient's clinical condition, goals achieved, those to be achieved, and the multidisciplinary
179 team's assessments."
- 180 • "Patients and their caregivers should be involved in defining the rehabilitation goals and the
181 individualized rehabilitation plan."

182

183 Statements are reported in Table 2.

184

185 Description

186 It is not possible to establish a single rehabilitation approach, and a number of rehabilitation treatment
187 modalities seem to provide benefits.^{45,66} Rehabilitation for children/adolescents affected by cancer
188 should be individualized,^{14,18,38,40,45,56,58,67,68} and the proposed activities should be enjoyable and
189 involve parents and siblings to improve compliance.⁵⁴ Rehabilitation adherence is greater when the
190 program is supervised by a physiotherapist.^{35,69} When rehabilitation is unsupervised and based on
191 counselling indications to be followed at home, monitoring treatment by filling out a diary, telephone
192 calls, and scheduled outpatient visits is recommended.⁶⁷ Exercise intensity ranges from low to
193 moderate and high, and is based on the subject's clinical condition and on the treatment phase.^{40,56,58,62}
194 In children/adolescents affected by cancer-related fatigue, performing physical activities and

195 relaxation is strongly recommended. Rehabilitation should include aerobic, strengthening, and
196 balance exercises.¹¹

197

198 **Leukemia**

199 The preliminary results reported in the literature on physical exercise in pediatric patients affected by
200 leukemia underline its beneficial impact on physical functioning, body composition, flexibility,
201 cardiorespiratory fitness, muscle strength, and QoL.^{34,38,40,41,56,70} For these patients, both preventive
202 and rehabilitation treatment are possible, depending on the phase of anticancer treatment:

203 - prevention in the active therapy phase: the physiotherapist should perform an interview before
204 treatment start to inform the patient about the possible onset of physical problems and the beneficial
205 effect of physical activity. An active lifestyle both during hospitalization and at home, based on the
206 child's/adolescent's interests, should be recommended. The information should be supported by
207 booklets or other types of materials. When lengthy hospitalization is expected (e.g., patients
208 undergoing hematopoietic stem cell transplantation, HSCT), an exercise program to maintain the
209 patient's functional abilities and muscle strength is indicated.⁷¹ This program should be individualized
210 and foresee the caregivers' involvement, and the patient's adherence should be monitored. During
211 the induction and the consolidation treatment phases, patients should perform regular low-intensity
212 physical activity, including aerobic training,^{38,40,55-58} stretching,³⁸ and strengthening exercises,^{38,40,56-}
213 ⁵⁹ to reduce the treatment's late side effects.⁵⁴

214 - Prevention in the maintenance and off-therapy phases: an interview with the child/ adolescent and
215 his/her family at the end of treatment should be scheduled to share information about the possible
216 physical impairments in the long time and the beneficial effect of physical activity. The
217 physiotherapist should encourage the patient to gradually start or resume physical activity or sport as
218 well as to maintain the most active lifestyle possible. In these phases the children/adolescents should
219 be referred to an exercise physiologist, if possible with specific expertise in and knowledge of
220 pediatric oncology, to favor the greatest adherence possible to a specific individualized exercise

221 program. During the maintenance phase, children/adolescents affected by acute lymphoblastic
222 leukemia should perform light-to-moderate activity (e.g., walking to school, biking, helping with
223 housework or gardening) for a few days a week. In this phase the goal should be to perform physical
224 activity daily to progressively achieve the activity levels suggested by the guidelines recommended
225 for healthy children/adolescents (Fig. 1).⁵⁴

226 During the maintenance phase of leukemia treatment, most of the studies suggest patients follow a
227 regular physical activity program that includes aerobic training, stretching, and strengthening
228 exercises.^{27,34,37,73}

229 - Prevention during HSCT is strongly recommended, with endurance and strengthening exercises to
230 reduce/minimize immobility and HSCT side effects and to improve quality of life.

231 - During the pre-transplant phase, it is recommended that a physiotherapist:

- 232 • explain to the child/adolescent and his/ her parents the benefits of engaging in a structured
233 physical activity program during the hospitalization phase of HSCT.
- 234 • give recommendations for specific rehabilitation, if necessary.

235 The exercise program during the inpatient phase of HSCT and after discharge should have a low-to-
236 moderate intensity, be individualized, and be supervised. The exercise program should include:

- 237 • endurance training
- 238 • strengthening, balance, coordination, and stretching exercises
- 239 • relaxation exercises
- 240 • rehabilitation counselling to promote functional mobility, with particular reference to body
241 moving, walking, and climbing stairs.¹⁰

242 - In children/ adolescents affected by chemotherapy-induced peripheral neuropathy (CIPN),
243 rehabilitation should focus on remediation of impairments (postural control deficits, gait
244 abnormalities, muscle weakness, loss of fine motor skills),⁷⁴ on supporting motor control skills
245 (jumping, running, stair climbing), and on promoting regular physical activity. Ankle-foot orthosis

(bracing) can be used to address loss of ankle range of motion (ROM), weakness, and associated gait abnormalities, with possible “weaning” of the orthoses after treatment end.⁷⁵ Custom foot orthosis should be prescribed to treat pain.⁷⁶ Gloves can be used to support hand function activities. In addition, patient/family education should also address loss of sensory function. In children who develop hypersensitivity to light touch, desensitization treatments may also be helpful.⁷⁷

- In children/adolescents with osteonecrosis, rehabilitation during nonoperative treatment should focus on protecting weightbearing, decreasing pain, and addressing functional impairments that limit mobility or exacerbate pain.⁷⁸ If necessary, the therapist provides and trains the child/ adolescent to use an assistive device, such as crutches or a wheelchair.²⁶ For patients with osteonecrosis of the shoulder, physical therapy should include full passive range of motion and pendulum exercises without active overhead exercises to prevent joint stiffness caused by disuse.⁷⁹ Patients with painful osteonecrosis may be treated with bracing, custom orthoses, or slings.⁸⁰

CNS tumors

The literature does not report any standard rehabilitation interventions for children/adolescents with CNS tumors; various treatments seem to provide benefits.⁴⁶ Some authors report the benefits of playful rehabilitation activities, associated or not with physiotherapy, such as hippotherapy, hydrokinetic therapy, active videogames, and aerobic physical activity.^{45,66,81,82} Neuromotor rehabilitation treatment of children/adolescents with CNS tumors is similar to that performed in other types of acquired brain injuries.

- In children/adolescents affected by ataxia, conventional physical therapy (e.g., strengthening exercises, balance training, practice of functional tasks) has shown to be beneficial.⁸³ Problem-based task training may help children and adolescents with CNS tumors to achieve functional improvements by facilitating motor control and the learning process.⁸⁴

- In children/adolescents with cerebellar mutism syndrome (CMS), long-term multimodal rehabilitation is frequently required. The presence of emotional, cognitive, and communication

272 problems requires integrating physical rehabilitation with speech and neuropsychological
273 rehabilitation.⁸⁵

274 - For children/adolescents with hemiplegia, research shows that constraint-induced movement
275 therapy in the post-acute phase may be beneficial to improve motor function.^{86,87}

276 - For children/adolescents with upper limb neuromotor deficits, a case series study found promising
277 results of a rehabilitation therapy program based on action observation.⁸⁸

278

279 **Bone cancer**

280 During the pre-surgical phase, the physiotherapist deals with the patient's functional rehabilitation,
281 identifying any pre-existing impairments providing recommendations, and performing a specific
282 treatment to improve function. Furthermore, the physiotherapist should help the children/adolescents
283 and their parents in this phase to identify achievable post-surgical treatment goals, since achieving
284 long-term goals depends on the patient's participation and compliance to rehabilitation.¹²

285 The most frequent localization of bones cancer (60%) is in the distal femur and proximal tibia; various
286 authors have investigated post-surgical rehabilitation after a reconstruction intervention with modular
287 prosthesis. Most of these studies are observational studies with a small sample size. There are
288 rehabilitation treatment protocols for the first month post-surgery according to the localization of the
289 tumor based on the different surgical approaches that these require. One study reported satisfying
290 results in most patients at 12 months post-intervention based on the Musculoskeletal Tumor Society
291 (MSTS) score. The rehabilitation protocol included ROM, strengthening, proprioceptive, and
292 autonomy recovery exercises.²⁰ There is a correlation between the muscle strength recovery of the
293 knee extensors, the knee flexion ROM, and functional recovery.⁶³ The subjects with the best ROM
294 recovery are those with the best outcomes in terms of functional performance and quality of life.⁶²
295 There are two treatment phases based on weight concession. In the first phase, active and passive
296 mobilization, strengthening, and proprioceptive exercises are proposed. In the second phase, with the
297 progressive concession of weightbearing, treatment focuses more on exercises in the standing

298 position, weight transfers, knee neuromotor control, and quadricep strengthening exercises in a closed
299 kinetic chain.²³ Various studies also considered gait analysis,^{45,60,64,65} underlining how frequently
300 these patients develop asymmetrical gait patterns with evident compensation strategies. It is necessary
301 to define a rehabilitation treatment plan that also enhances the strengthening of the contralateral
302 healthy limb.^{60,64}

303 Rehabilitation should be individualized and should focus on balance, core stability, and walking.²³
304 Surgery, which determines an extensive resection of bone and muscle tissues, causes sensorimotor
305 shock with proprioceptive afferences loss. In the long term there is no difference between the deep
306 sensitivity of the healthy limb and the contralateral limb.⁸⁹ Other authors have underlined that this
307 post-surgical condition determinates motor control loss with postural automatism deficit and the
308 patients' need to relearn a correct gait pattern.^{23,61} These results confirm the importance of balance,
309 proprioceptive, and motor control exercises in post-surgical rehabilitation.

310 Pediatric patients undergoing reconstruction with an extendable prosthesis should be followed over
311 time, with repeated rehabilitation cycles after the prosthesis length modification.⁹⁰ The literature
312 proposes different approaches:

- 313 ● exercises three times per week for a maximum of 60 minutes per session, for at least 10 weeks
314 before the intervention and for 10-12 weeks post-intervention.¹⁴
- 315 ● two-four sessions per week in the first six weeks, then one or two sessions per week for the next
316 six weeks.¹⁹
- 317 ● two sessions of 45 minutes per day during chemotherapy treatment (in this case, the literature
318 reports high adherence rates to rehabilitation).⁵³

319 No standardized rehabilitation protocols for patients affected by upper-limb bone tumors are available
320 in the literature in the literature. Two rehabilitation treatment schemes have been proposed for
321 localization in the humerus, the area surrounding the elbow, and the shoulder blade. Both treatments
322 aim to recover ROM, muscle strength, and upper limb function.^{12,19} There are no studies that indicate

323 an optimal rehabilitation modality, neither during hospitalization nor in the community. Many authors
324 agree on the importance of a personalized intervention.^{17,18,46,69}

325

326 Question 3: "How long should the patient be followed up?"

327 Recommendation:

328 "Rehabilitation should last as long as the subject's clinical condition requires, regardless of whether
329 in the hospital, community, or home setting."

330 The Statement is reported in Table 2.

331

332 Description

333 The panel of experts strongly recommend the continuity of rehabilitation between the hospital,
334 community, and home settings, at least for the duration of chemotherapy treatment.^{29,31,51,52}

335 Rehabilitation is required in the acute phase, before or after surgery, after discharge, and for those
336 admitted to rehabilitation specialist centers near home.¹³ Rehabilitation should continue in the
337 community⁶⁹ and should be integrated with the hospital rehabilitation service.⁹¹ To facilitate the
338 monitoring of patients over time, even during survivorship, it is appropriate to give them concise,
339 comprehensive documentation of previous treatments, such as the Survivorship Passport (SurPass),
340 elaborated by the Pan-European Network for Care of Survivors after Childhood and Adolescent
341 Cancer (PanCare) and by The European Society for Paediatric Oncology (SIOP Europe), in
342 collaboration with CINECA and European parent, patient, and survivor organizations.⁹²

343

344 **Conclusions and future directions**

345 It is difficult to provide evidence-based rehabilitation indications for pediatric patients affected by
346 cancer given the paucity and low quality of the literature currently available. In this context, expert
347 opinions mediated by the CC methodology is important to inform clinical practice. Some key points

348 regarding rehabilitation interventions have already been established, such as the importance of early
349 multimodal rehabilitation and the need to perform both preventive and rehabilitation interventions.
350 Preventive intervention should also consider the promotion of neuro-psychomotor development.
351 Family involvement is widely recognized as a fundamental aspect. Rehabilitation care should be
352 supervised, individualized, and aimed at achieving clinical outcomes and the patient's significant
353 goals. Rehabilitation tools should be age-appropriate, with an emphasis on play-based interventions
354 for children and on respecting the personal interests of adolescents. In the acute phase, rehabilitation
355 should be intensive and delivered according to the multidisciplinary team's indications. Physical
356 activity should be integrated with rehabilitation to promote the global physical and psychosocial
357 health in this population. The lack of strong evidence regarding physical therapy interventions in
358 children and adolescents affected by cancer, other than general physical exercise interventions,
359 remains a limitation of our work. There is the need to define some core outcome sets and related
360 outcome measures for different rehabilitation issues to allow a comparison between different studies.
361 Studies should also involve preschoolers and patients with a diagnosis other than acute lymphoblastic
362 leukemia, which is the most represented population in the literature. The relevance of a case series
363 study design should also be considered so as to inform future higher quality research. Further,
364 appropriate reporting checklists should be followed to improve the quality of reporting. Finally, when
365 there is a control group, it is often described only as "care as usual"; it must be better defined.

366

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368 All authors declare no conflicts of interest.

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676

677 **Legend list:**

678 Table 1: Summary of recommendations for rehabilitation of children and adolescents affected by
679 cancer.

680 Table 2: Summary of statements for rehabilitation treatment of children and adolescents affected by
681 cancer.

682 Supplemental Table 1/S#: Search strategies for the rehabilitation treatment of pediatric patients
683 affected by cancer.

684 Figure 1: The Council for Physical Education in Children (COPEC) of the National Association for
685 Sport and Physical Education (NASPE) recommendations.

686