EARLY-PHASE ADAPTATIONS TO INTRAHOSPITAL TRAINING IN STRENGTH AND FUNCTIONAL MOBILITY OF CHILDREN WITH LEUKEMIA

ALEJANDRO F. SAN JUAN,1 STEVEN J. FLECK,2 CAROLINA CHAMORRO-VIÑA,1 JOSÉ L. MATÉ-MUÑOZ,1 SUSANA MORAL,2 JAVIER GARCIA-CASTRO,2 MANUEL RAMÍREZ,3 LUIS MADERO,3 AND ALEJANDRO LUCIA2

1Exercise Physiology Laboratory, European University of Madrid, Madrid, Spain; 2Sport Science Department, Colorado College, Colorado Springs, Colorado 80903; 3Department of Haematology and Bone Marrow Transplantation, Children’s Hospital Niño Jesús, Madrid, Spain.

ABSTRACT. San Juan, A.F., S.J. Fleck, C. Chamorro-Viña, J.L. Maté-Muñoz, S. Moral, J. García-Castro, M. Ramírez, L. Madero, and A. Lucia. Early-phase adaptations to intrahospital training in strength and functional mobility of children with leukemia. J. Strength Cond. Res. 21(1):173–177. 2007.—Improvements in chemotherapy and radiotherapy have contributed to the high survival rate (~70%) of childhood acute lymphoblastic leukemia (ALL). However, during treatment, lack of physical activity and treatment cause various short- to long-term side effects, such as muscle atrophy and physical deconditioning. The purpose of this study was to determine the effects of an intrahospital, short-duration (8 weeks) exercise training program on muscle strength and endurance and functional mobility of children with ALL. Seven children (4 boys and 3 girls; 4–7 years of age) who were in the maintenance phase of treatment for ALL were selected as subjects. Three training sessions of 90- to 120-minute duration were performed each week. Each session included 11 different strength exercises engaging the major muscle groups and aerobic training. Gains in strength and endurance were assessed with a 6 repetition maximum test for upper (seated bench press and seated lateral row) and lower extremities (leg press). Gains in functional mobility were assessed with the time up and go test (TUG) and the timed up and down stairs test (TUDS). Performance was significantly improved after the training program in all strength tests (p < 0.01 for seated bench press and p < 0.05 for both seated lateral row and seated leg press) and in the TUG test (p < 0.05). In summary, a period of time as short as 8 weeks is enough to produce clinically relevant early-phase adaptations in children receiving treatment against ALL (i.e., improved functional mobility and muscle strength). Although more research is needed in the area of exercise training and pediatric cancer, exercise sciences can play a beneficial role in assisting both oncologists in treating cancer and improving children’s quality of life during and after treatment.

KEY WORDS. resistance training, aerobic training, cancer

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for ~26% of all childhood cancers. Improvements in treatment techniques, such as combination chemotherapy and radiotherapy, have contributed to the high survival rate (~70%) now seen in the treatment of children with ALL (20). These therapies, unfortunately, may directly impact children’s future quality of life (QOL) through various short- to long-term side effects, which include anthracycline-induced cardiotoxicity, osteopenia, and, especially, muscle atrophy (4, 20, 29).

Although extensive research has been conducted on the beneficial effects of exercise training for adults with and survivors of cancer (5, 19) and some studies have specifically assessed the effects of strength training in this population (1, 6, 7, 15, 16, 22, 25, 26), considerably less research has been conducted in children with cancer (10, 21). We are unaware of a study specifically assessing the effects of a supervised conditioning program including both resistance and aerobic training in children with ALL. In healthy children, including prepubescents, resistance training does increase strength and has other health benefits (23, 28, 30). If appropriate training guidelines are followed (i.e., qualified instruction, competent supervision, and an appropriate progression of the volume and intensity of training), regular participation in a conditioning program including strength training has the potential in healthy children to increase bone mineral density, improve motor performance skills, and enhance physical capacity and overall health and fitness status (9, 12, 23). Although generally, long-term training or even life-long physical activity should be the goal of healthy and diseased populations, early-phase adaptations to short-term exercise training can give the patients positive feedback concerning their strength, aerobic fitness, and QOL and encourage the patients to pursue longer-term training. The finding that even a few weeks of regular exercise might be sufficient to bring about positive physiologic adaptations that help children cope with the anti-cancer treatment and its deleterious side effects would be a very positive finding for this population and the children’s parents.

Therefore, the purpose of this study was to determine if a short-term (8 week) intrahospital-supervised, conditioning program including both resistance and aerobic type training improves dynamic muscle strength of the upper and lower extremities and functional mobility in children receiving treatment for ALL. Based on previous research with adults (1, 6, 7, 15, 16, 22, 25, 26) and children (21), we hypothesized that this type of program would have a significant beneficial effect on the aforementioned variables.

METHODS

Experimental Approach to the Problem

An intrahospital gymnasium designed for use by children during treatment against ALL (Children’s Hospital Niño Jesús of Madrid, Department of Onco-Haematology and Bone Marrow Transplantation, Madrid, Spain) (20) was where all physical conditioning was performed. Among
other equipment, the gymnasium includes pediatric (specifically built for the body size of children) weight training machines (Stride, Inc., Canonsburg, PA) and bicycle ergometers (Rhyno Magnetic H490; BH Fitness Proaction, Vitoria, Spain). This setting allows us to determine the effects of specific, supervised resistance and aerobic training on the strength and functional mobility of children being treated against ALL.

For this first pilot study, we chose to assess the short-term effects of a conditioning program in children in the last phase of the treatment (i.e., the so-called “maintenance phase” [6]) against ALL, because those undergoing the earlier, more aggressive phases of treatment frequently experience 1 or more complications (tumor recurrence, marked anemia, infections, etc.) that could considerably compromise adherence to the program. For the same reason, we did not study children who had undergone bone marrow transplantation because, in this subpopulation of children with ALL, treatment complications and side effects and tumor recurrences are frequent. We chose to study children of a very young age (4–7 years) because no study on physical activity and cancer has assessed children during this early, critical phase of life and because we felt it useful to “untrack” or target sedentary habits that will have deleterious health consequences later in life.

Dependent variables were (a) performance in functional tests that reflect children’s ability to perform important physical abilities of daily living such as normal gait (i.e., the time up and go test [TUG]) (18) or navigating stairs (the timed up and down stairs test [TUDS]) (10) and (b) dynamic muscle strength and endurance as measured by 6 repetition maximum (6RM) lifting ability of both the upper (seated bench press and seated lateral row) and lower body (leg press) (17). We chose to assess dynamic muscle strength and endurance instead of maximal dynamic muscle strength because, although improvements in the ability to perform maximal strength tests are of interest for athletic populations, they would be of little practical relevance for children under treatment for ALL, in whom maximal strength is not a main determinant of their ability to perform physical activities of daily living, which are mostly submaximal-strength tasks (e.g., climbing stairs, sitting, and rising from a chair, etc.). Additionally, determination of maximal strength or 1RM strength is not recommended in healthy children (2) and therefore would not be advisable in children suffering from diseases such as ALL.

Although originally 1 goal was to assess a control group of age- and sex-matched children receiving the same treatment against ALL, it was not possible to find such a group, because none of the numerous parents contacted gave their permission to perform several strength and functional tests on their children given that they were not going to enter any type of interventional training program, despite being required to undergo a tedious (4- to 6-week duration) familiarization period (as detailed below). To this end, nonhospitalized children who do not have to visit the hospital more than 1 or 2 times per month would have been required to visit the hospital on several occasions over a 4- to 6-week period despite not enjoying the benefits of a supervised conditioning program. Thus, although a control group would have strengthened the experimental design, for ethical and logistic reasons, it was not possible to test a control group. Testing a control group would have been possible if the thorough familiarization process had not been included in the study’s design, which would have significantly altered the validity and reliability of our measurements of strength and functional mobility. Despite the lack of a control group, the study does present the first data on young children performing a physical conditioning program while undergoing treatment for ALL.

**Subjects**

Before entering the study, informed consent was obtained from each participant’s parents, and consent was obtained from each participant. The study was approved by the local Human Investigations Committee and Review Board. A preliminary screening for subject selection was performed in the medical database of the Onco-hematology Department at Children’s Hospital Universitario Niño Jesús (Madrid, Spain). A total of 26 medical records of children treated for ALL in the aforementioned hospital were examined. After the oncologist treating each patient provided consent, subjects were deemed eligible for the study if they met each of the following conditions: (a) undergoing the last phase of maintenance therapy against standard-medium risk ALL following the ALL-BFM 95 protocol, which does not require hospitalization (6), (b) time elapsed after start of treatment ranging between 18 and 24 months, (c) nonobese with a body mass index (BMI) of < 25 kg·m⁻², (d) 4–7 years of age and within Tanner’s stage 1 of maturation status, (e) having no condition that could contraindicate vigorous physical activity, such as severe anemia (hemoglobin < 8 g·dl⁻¹), fever > 38°C, severe cachexia (loss of >35% premorbid weight), platelet count < 50 × 10⁹·µl⁻¹, neutrophil count ≤ 0.5 × 10⁹·µl⁻¹, or anthracycline-induced cardiotoxicity (20), and (f) currently living with their parents in Madrid, Spain.

Seven children (4 boys and 3 girls; age: 5.1 ± 1.2 [SD] years; weight: 24.0 ± 5.8 kg; height: 114.6 ± 7.7 cm) met all the above-mentioned eligibility criteria and were included in the study. Their clinical characteristics are shown in Table 1. The maintenance therapy they were receiving consisted of daily mercaptopurine (50 mg·m⁻²·d⁻¹) and weekly methotrexate (20 mg·m⁻²·wk⁻¹) (6).

### Table 1. Clinical characteristics of the children with acute lymphoblastic leukemia.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Time (mo) elapsed since start of treatment</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Boy</td>
<td>6 yr, 7 mo</td>
<td>24</td>
<td>Medium</td>
</tr>
<tr>
<td>B</td>
<td>Boy</td>
<td>5 yr, 9 mo</td>
<td>24</td>
<td>Standard</td>
</tr>
<tr>
<td>C</td>
<td>Boy</td>
<td>7 yr, 4 mo</td>
<td>22</td>
<td>Medium</td>
</tr>
<tr>
<td>D</td>
<td>Girl</td>
<td>4 yr, 7 mo</td>
<td>21</td>
<td>Standard</td>
</tr>
<tr>
<td>E</td>
<td>Girl</td>
<td>4 yr, 4 mo</td>
<td>20</td>
<td>Standard</td>
</tr>
<tr>
<td>F</td>
<td>Boy</td>
<td>5 yr, 5 mo</td>
<td>18</td>
<td>Medium</td>
</tr>
<tr>
<td>G</td>
<td>Girl</td>
<td>6 yr, 3 mo</td>
<td>24</td>
<td>Standard</td>
</tr>
</tbody>
</table>

**Dynamic Strength and Endurance and Functional Tests**

None of the subjects had ever participated in a weight-training or conditioning program before the study. To minimize the influence of a possible learning effect (caused by improvement of technique and coordination and/or diminishment of muscle inhibition) (11) and thus to stabilize the initial test results before the start of the study, all subjects underwent a familiarization period of 4–6 weeks. A warm-up period including aerobic and...
strengthening exercises (~10 minutes), and a specific warmup preceded each test for the test–retest assessment.

Very high intraclass correlation coefficients ($R \geq 0.974$; $p < 0.001$) between repeated tests were shown for all the tests that are described below, i.e., $R = 0.995$ ($p < 0.001$) for seated bench press, $R = 0.997$ ($p < 0.001$) for leg press, $R = 0.977$ ($p < 0.001$) for seated lateral row, $R = 0.989$ ($p < 0.001$) for the TUDS test, and $R = 0.974$ and $R = 0.997$ ($p < 0.001$) for the TUG 3 and 10 m, respectively. Using the same tests and equipment in older children of both sexes ($N = 7$; mean age: $10 \pm 1$ years) being treated in the same hospital against several types of cancer, we have obtained similar results indicative of high test–retest reliability and precluding any potential learning effect ($R \geq 0.989$ and $p < 0.001$ for all tests).

Dynamic upper-body muscle strength endurance was measured using a seated bench and a seated lateral row machine (Strive, Inc.), and dynamic lower-body muscle strength endurance was measured with a seated leg press machine (Strive, Inc.). The 6RM value was measured in kilograms and is described as the maximum strength capacity to perform 6 repetitions until momentary muscular exhaustion. The testing protocol consists of 3 warm-up sets at 50, 70, and 90% of the perceived 6RM separated by 1-minute rest periods. A 2-minute rest period followed the last warm-up set, after which a 6RM attempt was made at 100–105% of perceived 6RM depending on the effort needed to perform the last warm-up set at 90% of the perceived 6RM. If the first 6RM attempt was successful, the resistance was increased 2.5–5%, and after 2 minutes of rest, another 6RM attempt was made. If the second 6RM attempt was successful, a second testing session was scheduled after 24 hours of rest. If the first 6RM attempt was not successful, the resistance was decreased 2.5–5%, and after 2 minutes of rest, another 6RM attempt was made. If the second 6RM attempt was successful, the weight used was the 6RM. If the second 6RM attempt was not successful, another testing session was scheduled after 24 hours of rest. Each subject was instructed to perform each exercise to momentary muscular exhaustion. Any repetitions not performed with a full range of motion were not counted.

To measure children’s functional mobility, we used the TUG test of 3 and 10 m (18) and the TUDS test (10). Both types of tests have been shown to be reliable and valid in healthy children and also in children with various diseases or disabilities (10, 13, 21). The TUG 3 and 10 m tests are measures of the time needed to stand up from a seated position in a chair, walk 3 and 10 m, respectively, turn around, return to the chair, and sit down. For the TUDS, we measured the time it took the children to ascend and descend 12 stairs (10). All the children used the railing in all the tests. The use of a railing while ascending and descending the stairs was allowed to diminish the risk of falling. Performance time in all the tests was measured by the same investigator with the same stopwatch to the nearest 0.1 second.

All the tests were performed at the same time of the day (9:00 AM to 11:00 AM) under similar environmental conditions (20–24°C, 45–55% relative humidity). All the children consumed their usual breakfast (cereals, milk, and fruit juice) 3 hours before all testing sessions.

**Exercise Program**

All the children followed an 8-week training program, consisting of 3 weekly sessions with a duration ranging from 90 (in the first few weeks of the program) to 120 minutes (by the end of the program). Each session started and ended with a low-intensity 15-minute warm-up and cool-down period, respectively, consisting of cycle-ergometer pedaling at very light workloads and stretching exercises involving all major muscle groups. The core portion of the training session was divided into strength and aerobic exercises.

Strength training included 11 types of exercises engaging the major muscle groups (bench press, shoulder press, leg extension, leg press, leg curl, abdominal crunch, low back extension, arm curl, arm extension, seated row, and lateral pull-down). For each exercise, the children performed 1 set of 8–15 repetitions (total of ~20-second duration). Each exercise was separated from the next one by a 1- to 2-minute rest period with stretching exercises of the muscles involved in the previous exercise (3, 12). The load was gradually increased as the strength of each child improved. Aerobic exercises consisted of pedaling on a cycle-ergometer, running, walking, and ‘aerobic games’ involving large muscle groups (i.e., jumping exercises, ball games, group games). The duration and intensity of the aerobic training was gradually increased (9) during the 8-week period so that the subjects started with at least 10 minutes of aerobic exercises at 50% of age-predicted maximum heart rate (HRmax) and were able to achieve at least 30 minutes of continuous exercise at ≥70% HRmax by the end of the program. All the children wore a portable heart rate meter during the sessions to monitor their exercise intensity. Aerobic and group games were necessary to maintain and improve the children’s adherence to the training program (i.e. by making every session different, the children’s interest and motivation was maintained). All the sessions were supervised by exercise physiologists and qualified fitness instructors (1 instructor for every 2 children). A pediatrician was also present in each of the training sessions.

Each child was evaluated by his/her oncologist in the outpatient clinic every 2 weeks over the training period with a complete hematologic and biochemical analysis and a thorough physical evaluation. Finally, over both the familiarization and training period, all the children and their parents were instructed to follow the children’s usual nutritional habits. None of them were taking any nutritional supplement during the aforementioned periods. A questionnaire on food intake frequencies (24) was administered to the children’s parents at the end of the training period to record children’s mean dietary habits corresponding to this period. The results showed that the dietary pattern of the participants was similar to that of Spanish children in general (27), i.e., mean intake frequency (in times per week) of 12.6 ± 2.2 for cereals, 13.3 ± 5.4 for fruits, 6.3 ± 1.4 for vegetables, 12.1 ± 1.0 for meat, fish, and eggs, 24.8 ± 2.7 for milk products, 4.2 ± 1.9 for fat and oils, and 3.4 ± 1.1 for sweet foods.

**Statistical Analyses**

Statistical analyses were performed with SPSS (version 11.5; SPSS, Inc., Chicago, IL). The Wilcoxon test was used to assess the effect of the training program on the variables tested (strength: seated bench press, seated row, and leg press), and functional muscle performance (TUDS, TUG 3 and 10 m) by comparing the mean values obtained before and after training. The level of significance was set at 0.05. Results are expressed as mean ± SD.
RESULTS
Adherence to Training and Possible Adverse Effects
Adherence to training was >85% in all subjects (i.e., >20 of a total of 24 training sessions). None of the subjects missed more than 2 consecutive training sessions. No major adverse effect and no major health problem were noted in the subjects over the 8-week period (i.e., hematologic and biochemical blood parameters remained within normal limits and children’s physical examinations revealed no abnormality).

Performance During Functional and Strength Tests
Except for the TUDS test, mean subject’s performance significantly improved during the functional and strength tests ($p < 0.01$ for the seated bench press test and $p < 0.05$ for the seated lateral row, seated leg press, TUG 3 m, and TUG 10 m; Table 2). A higher posttraining value was found in all the subjects for the seated bench press, seated lateral row, and bench press test. Except in 1 subject, all individual values of performance were also improved in the TUG 3 m and TUG 10 m tests. Three subjects did not show an improvement in the TUDS test.

DISCUSSION
Our study shows that a short-duration (8 week) intrahospital-structured, supervised training program combining cardiorespiratory and resistance exercises positively affects changes in muscle strength and endurance of the upper and lower extremities and functional mobility in very young children (4–7 years) receiving maintenance therapy against ALL. To our knowledge this is the first attempt to assess this question in very young children. Thus, it is difficult to directly compare our results to those of previous studies training children being treated against ALL.

Marchese et al. (21) observed, in an older group of children (age, 4–18 years) receiving treatment against ALL, that a 16-week physical therapy intervention program combined with home-based exercises (aerobic training, stretching exercises) caused significant improvements in ankle dorsiflexion range of motion and knee extension strength. However, such training effects were not accompanied by significant improvements in functional mobility (i.e., no improvement in the TUDS test). In contrast, our shorter, supervised training program consisting of both resistance and aerobic training did induce significant improvements in both muscle strength and endurance and functional mobility (TUG 3 and 10 m) of younger children with ALL. Thus, strength gain was also associated with improvements in the functional ability to perform measures of daily living tasks.

The baseline strength values found in our children cannot be compared with those reported by Gocha Marchese et al. (10) in children with ALL (age, 4–15 years) because both measuring instruments and evaluation tests differed between studies (i.e., dynamometer and 1RM test in their study vs. 6RM using specific weight training machines in ours). Gocha Marchese et al. (10) did not study strength of the upper extremities, whereas we did study strength of both lower (leg press) and upper extremities (using both seated bench press and seated lateral row). They assessed strength of knee extension and ankle dorsiflexion, whereas we used a test of muscle strength and endurance in a seated leg press machine (i.e., engaging several large muscle groups). We chose to assess dynamic muscle strength and endurance (6RM) instead of maximal dynamic strength to obtain results of practical relevance for children with ALL, in whom maximal strength is not a major determinant of their ability to perform physical activities of daily living, which are mostly submaximal-strength tasks (e.g., climbing stairs, sitting and rising from a chair).

We also found significant improvements in the TUG 3 m and TUG 10 m tests after the exercise program intervention. Our posttraining mean value in the TUG 3 m is similar to that reported in the noninterventional study by Gocha Marchese et al. in children treated against ALL before delayed intensification therapy (10) even though our subjects were considerably younger (9–10 vs. 5 years in our study). Gocha Marchese et al. did not, whereas this study did, use the longer TUG 10 m. Although statistical significance was not reached, we found a tendency towards an improvement in the TUDS test, indicating it may be more difficult to bring about a significant change in this measure of daily life activity or that a training program of longer duration might be necessary to obtain significant improvements in this measure. Concerning the TUDS test, it must be noted that the baseline values of our subjects are slightly higher than those previously reported in children of a wide age range (4–18 years) with ALL both before and after a physical therapy intervention program (21).

Our findings are of clinical relevance because muscle weakness and subsequent impaired functional mobility are frequent complications of the treatment against childhood ALL (20, 29). Thus, the significant improvement we found in global strength and endurance (i.e., large muscle groups of upper and lower extremities) and functional mobility with only 8 weeks of training should be considered in the prescription of exercise for young children being treated against ALL. Future controlled studies should assess both the short- and long-term effects of the type of supervised exercise program used here on the strength, functional capacity, and aerobic capacity and QOL of children with ALL during maintenance therapy and also earlier in treatment. In addition, it would be worthwhile to study children with ALL who have undergone bone mar-

### Table 2. Mean ± SD values (pre- vs. post-exercise training) of performance in strength and functional tests in the study subjects ($N = 7$).

<table>
<thead>
<tr>
<th>Performance in each test</th>
<th>Pretraining</th>
<th>Posttraining</th>
<th>Difference (post- vs. pretraining)</th>
<th>95% CI for difference</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seated bench press (kg)</td>
<td>24.0 ± 5.5</td>
<td>30.1 ± 8.0</td>
<td>6.1 ± 1.3</td>
<td>2.9, 10.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Seated leg press (kg)</td>
<td>17.4 ± 6.0</td>
<td>21.7 ± 6.0</td>
<td>4.3 ± 2.9</td>
<td>1.7, 6.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Seated lateral row (kg)</td>
<td>59.9 ± 20.0</td>
<td>66.1 ± 23.7</td>
<td>6.2 ± 3.5</td>
<td>1.2, 14.6</td>
<td>0.05</td>
</tr>
<tr>
<td>TUG-3 m (s)</td>
<td>8.3 ± 1.3</td>
<td>7.9 ± 0.9</td>
<td>-0.4 ± 0.6</td>
<td>-0.38, -0.22</td>
<td>0.12</td>
</tr>
<tr>
<td>TUG-10 m (s)</td>
<td>13.7 ± 1.7</td>
<td>12.7 ± 1.3</td>
<td>-1.0 ± 0.9</td>
<td>-2.2, -0.1</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*TUG = time up and go test; TUDS = timed up and down stairs.*
row transplantation (BMT) as part of the treatment against ALL because BMT is commonly associated with severe muscle weakness and physical deconditioning (e.g., because of aggressive treatment with corticosteroids after surgery) (29). Finally, future research should determine the molecular mechanisms (e.g., neuroendocrine adaptations, increased secretion of skeletal muscle growth factors) that are ultimately responsible for the beneficial effects of supervised exercise training in young children with ALL. Future studies focusing on the potential mid- or long-term effects of exercise training on the immune system function and incidence of tumour recurrence in patients/survivors of childhood ALL would also be worthwhile. At least in adults, the nonspecific immune system may be improved by physical activity, possibly through the additive effects of repeated exercise bouts (14). As a result, regular exercise could potentially decrease the risk of some types of cancer, such as breast or colon cancer.

**Practical Applications**

In summary, children of very young age (4–7 years) receiving the last phase of treatment against ALL can safely undergo an intrahospital-structured, supervised conditioning program of both aerobic type training and resistance exercise training engaging large muscle groups (i.e., using pediatric weight lifting machines). The data presented here suggest that this type of training does improve their QOL. A period of time as short as 8 weeks is enough to produce clinically relevant benefits (i.e., improved functional mobility and muscle strength). Although more research is needed in the area of exercise training and pediatric cancer, sport science professionals (fitness instructors, exercise physiologists, etc.) should be aware of their potentially valuable task in (a) assisting oncologists in the management of children under treatment and (b) helping children cope with anti-cancer treatment.

**References**


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Address correspondence to Alejandro Lucia, alejandro.lucia@uem.es.