Treatment of Neuromuscular Scoliosis in Young Children With Severe Spastic Cerebral Palsy: A Systematic Review of the Literature

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ABSTRACT

Introduction: Children with GMFCS IV and V spastic cerebral palsy (CP) are at risk of developing early-onset scoliosis (EOS). There is no agreement about treatment for very young children (less than 5 or 6 years old). This systematic review focuses on this problem. Materials and Methods: We conducted a search in the PubMed, Scholar Google, Cochrane Library, BVS/BIREME, LILACS, and SCIELO databases from 1/2009 to 11/2020, using the following keywords: “cerebral palsy,” “scoliosis,” “early-onset,” “treatment”. We eliminated duplicated articles, those with unrelated research, without complete text, with very few spastic CP patients or patients aged over 6, and without clear etiology or results. The variables evaluated in the selected articles were: level of evidence, average age, GMFCS level, deformity types, treatments, follow-up, outcomes, and complications. Results: From the 6770 articles retrieved, only 10 were included: 8/10 with evidence level IV, average ages 3.2 to 10 years old, scoliosis as prevalent deformity, average follow-up 1.5 to 9.8 years. Treatment: traditional growing rods (3), magnetic growing rods (1), early instrumented fusion (2), casting (1), orthotics (2), and VEPTR (1). Early instrumented fusion provides ≥ 75% of Cobb correction; growing rods, orthotics, and VEPTR, between 25 and 50%, and plaster casts only prevent progression. Non-surgical treatments have a lower rate of complications (5.8%-36%) than surgical ones (21.5% - 73.1%). Surgical complications and postoperative mortality are higher in spastic than in hypotonic patients. Conclusions: Surgery is not a good initial option in very young children with spastic, GMFCS IV-V CP.

Keywords: Cerebral palsy; spasticity; scoliosis; early-onset; treatment.

Level of Evidence: III
costal expandible de titanio, el 25-50%, y los yesos solo logran mantenerla. La tasa de complicaciones es menor en los tratamientos incruentos (5,8-36%) que en los quirúrgicos (21,5-73,1%). Las tasas de complicaciones quirúrgicas y de muerte poscirugía en espásticos son mayores que en hipotónicos. Conclusiones: La cirugía no es buena opción inicial para las escoliosis de comienzo temprano en niños pequeños con parálisis cerebral espástica, nivel IV y V del GMFCS.

Palabras clave: Parálisis cerebral; espasticidad; escoliosis; comienzo temprano; tratamiento.

Nivel de Evidencia: III

INTRODUCTION

Cerebral palsy (CP) is a childhood disease in which there is a motor disorder caused by a static, non-progressive lesion of the brain,1 and it is one of the disorders that cause the development of a neuromuscular scoliotic deformity in the affected child. The worldwide prevalence of CP is around 2.11 per 1,000 live births and has remained constant despite healthcare changes.2

Neuromuscular scoliosis in patients with CP is one of the deformities that can appear in an early stage of life,3-6 and is included within ‘early-onset scoliosis’ (EOS).7 The age was extended by the Scoliosis Research Society to include all curves that appeared before the age of 10.7 The early onset of scoliosis in a patient with CP is, as is known, one of the major risk factors for its progression.8 But the most important isolated risk factor is the degree of neurological involvement.9,10 The higher the level of the Gross Motor Function Classification System (GMFCS),3 the more prevalent it is, and it is maximum at GMFCS level V with severe general involvement.3,6

The natural evolution of EOS depends on the etiology of the deformity, but it is never good, regardless of it.11 In turn, the natural evolution of neuromuscular scoliosis shows that age is an important risk factor for progression:12 the earlier the onset, the greater the risk of aggravation and of leading to a very serious deformity during growth.

Treatment for EOS with curves <50°-60° is serial casting and orthoses and, for curves greater than these values, surgery. There are different surgical systems, such as traditional growing rods (TGR), magnetic growing rods (MGR), growth-guided systems (Shilla), vertical expandable prosthetic titanium ribs, among others.13

However, the treatment of EOS is generally complicated and controversial, since it covers a non-homogeneous population, often with significant comorbidities. The is no consensus on the treatments for each particular case of EOS,14 there is a lot of variation and differences among surgeons in deciding whether or not the treatment should be surgical15 and, if so, what is the appropriate technique for each type of EOS.16 Ultimately, the decision on the type of treatment depends on the underlying diagnosis, the condition of the spine and chest wall, and the type of instrumentation available or preferred.15

In recent years, new surgical technologies have emerged intending to improve outcomes and reduce complications. Even so, surgeries cause high morbidity and mortality and unplanned secondary interventions.17,18 In the particular case of EOS in children with spastic CP, this is even more complex due to concomitant pelvic obliquity or neurological dislocation of the hips, which imposes real therapeutic dilemmas.19

The objective of this research was to carry out a systematic review of the literature of the last 11 years to assess whether there is a more effective method with fewer complications for the management of neuromuscular EOS in young children (<5-6 years) with spastic CP.

MATERIALS AND METHODS

We searched in the following literature databases: PubMed, Google Scholar, Cochrane Library, VHL (Virtual Health Library)/BIREME, LILACS and SciELO. Articles published on the subject were searched between January 2009 and November 2020 (11 years), using the following descriptors: “cerebral palsy, scoliosis, early-onset, treatment”. All articles in Spanish, English, French, Italian and Portuguese were initially included.

Selection criteria

Duplicate articles were first eliminated and a selection was made by title linked to the research topic. Studies with access to the full text of the article were then identified. Previous systematic reviews, meta-analyses and comparative articles were then removed, although they were considered for discussion. Finally, articles with a very small number of patients with spastic CP or without this condition, those without discrimination of etiology, those...
that did not show results and those that included elderly patients were discarded. Following the objective of the research, the remaining studies were analyzed in search of articles only with patients with spastic CP and EOS, and those on EOS in general, but with a good proportion of CP.

Thus, the articles selected were evaluated by analyzing the following variables: type of study, level of evidence, number of cases, average age, GMFCS level, type of deformities, treatments used, follow-up, outcome, rate and type of complications (evaluated according to the classification of Smith et al.).

RESULTS
Selection of studies

Figure 1 shows the case selection flowchart. 6770 articles were found. After eliminating duplicates and choosing by title linked to the research objective, 202 articles remained. Reading the abstracts discarded 29 more articles, leaving 173. Of these, only 75 were complete articles with access to the full text, and were considered included in the review. Twenty-one previous systematic reviews, meta-analyses, and comparative studies were discarded. Of the rest, 44 were eliminated because they did not have patients with CP or because of the low number of cases or because they did not discriminate the pathophysiological type, did not identify the type of EOS, did not show the results, or included elderly patients. The final selection yielded 10 articles that were included in this review: we obtained only two studies dedicated to exclusively evaluating neuromuscular-type EOS treatments of patients with spastic CP. The remaining eight clinical research studies on EOS were included because they had a good number of CP patients to be analyzed (Figure 1, Table).

Figure 1. Paper selection processes.

'McElroy 2012, Ramirez 2020'
### Table. Analysis of variables of the papers selected and included in the review.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Papers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>Ramirez et al., 2020&lt;sup&gt;22&lt;/sup&gt; Studer et al., 2019&lt;sup&gt;23&lt;/sup&gt; Nakamura et al., 2014&lt;sup&gt;24&lt;/sup&gt; Yaszay et al., 2017&lt;sup&gt;25&lt;/sup&gt; Mathews et al., 2016&lt;sup&gt;26&lt;/sup&gt; Helenius et al., 2018&lt;sup&gt;27&lt;/sup&gt; Sitoula et al., 2016&lt;sup&gt;28&lt;/sup&gt; Oyoun and Stuecker, 2014&lt;sup&gt;29&lt;/sup&gt; McElroy et al., 2012&lt;sup&gt;30&lt;/sup&gt; LaValva et al., 2020&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td>Type of study</td>
<td>Retrospective case series Retrospective case series Therapeutic (case series) Retrospective case series Comparative study of moderate and severe cases Retrospective case series Retrospective case series Retrospective case series</td>
</tr>
<tr>
<td>Level of Evidence</td>
<td>IV IV IV IV III IV IV IV III</td>
</tr>
<tr>
<td>Number of cases of spastic/neuromuscular CP 20/67 5/30 (&lt;10 years) 38/52 14 79 CP/180 214 (68 NM/214 = 14 CP68)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>6.2 ± 2.1 6 (3.5-7.5) 9.7 (8.3-10.8) 9 5.6 8.3 (4.4-9.9) 8.9 (4-12) 7.6 (5.2-10) 3.2 ± 1.9</td>
</tr>
<tr>
<td>GMFCS</td>
<td>NS NS V IV and V I-V NS NS (2) / V (31) NS NS NS</td>
</tr>
<tr>
<td>Deformity</td>
<td>Scoliosis Scoliosis Scoliosis Scoliosis Scoliosis Scoliosis Scoliosis Scoliosis Scoliosis Scoliosis</td>
</tr>
<tr>
<td>Treatment</td>
<td>Double GR (rib-pelvis construct) MGR (MAGEC model) DSB Corset Instrumented early fusion DEFO GR Definitive instrumented arthrodesis Eiffel Tower VEPTR GR (4 single/23 double) Serial plaster casting</td>
</tr>
<tr>
<td>Average follow-up (months)</td>
<td>NS NS 20.8 24-36 18 72 117.6 16 57.6 46.8</td>
</tr>
</tbody>
</table>
| Outcome assessment tools used | Cobb angle, complications NS Cobb angle, progression, Bridwell et al. questionnaire Cobb angle, PO, CPCHILD Cobb angle, chest and spine height, balance Cobb angle, PO Cobb angle, PO, lumbar and thoracic spine height, SAL, balance Cobb angle, T1-S1 length, SAL, and PO Cobb angle, DCVA, T1-T12 length, L1-S1 length Cobb angle, DCVA, T1-T12 length, L1-S1 length |}

**Results**

- Lower % of correction of the frontal and sagittal Cobb angle in spastic patients (without statistical differences) 63/59 46% progress <10°, 100% acceptance of the questionnaire
- None required revision due to Cobb angle correction 30-47% increase in spine height 30-40% increase in chest height +30% to -29% front alignment modification 52-67% improvement in sagittal alignment
- 77% scoliosis correction 15° (average) PO correction
- Scoliosis improvement of 24-43.5% 18-20% increase in spinal height 58.4% PO improvement 51.9% T1-S1 height improvement 116%
- Equal angular value of curves No changes in DCVA 8% increase in T1-T12 length 10% increase in L1-S1 length

- % of complications 73.1% spastic vs. 53.7% hypotonic 40% of patients 5.8% of patients 21.5% of patients NS 26% (severe) vs. 19% (moderate) complications/patient
- 28.2% mortality at 5.6 years after surgery 45% of patients 70.4% of patients 36% (NS in CP)
- Severity/type according to Smith et al. IIA, IIB IIA, IIB IIA, IIB IIA, IIB IIB, III NA
- Complications Infection, mechanical problems and failures, postoperative pain, pneumonia, death Infection, proximal extension of instrumentation Skin problems Infection, implant-related complications Infection, Distant postoperative death Infection, implant-related complications Skin problems, bedsores, digestive disorders, discomfort, hygiene

**GR** = growing rods, **MGR** = magnetic growing rods, **CPCHILD** = Caregiver Priorities and Child Health Index of Life with Disabilities, **DCVA** = difference in the costovertebral angle, **DEFO** = dynamic elastomeric fabric orthosis, **DSB** = dynamic spinal brace, **SAL** = space available for the lung, **GMFCS** = Gross Motor Function Classification System, **MAGEC** = Magnetic Expansion Control (Nuvasive, San Diego, California, USA), **NA** = not applicable, **NS** = not specified, **NM** = neuromuscular, **PO** = pelvic obliquity, **CP** = cerebral palsy, **VEPTR** = vertical expandable prosthetic titanium rib, **TLSO** = thoracic lumbar sacral orthosis.
Eight of the 10 studies have level IV evidence, except for that of Helenius et al.\textsuperscript{28} and LaValva et al.\textsuperscript{30}, which are level III.

**Assessment of the methodology**

The number of patients with spastic CP in the different studies is very varied, as are the average ages, between 3.2 and 10 years. Only one study included only patients with level V of the GMFCS (107 cases); other three studies had patients with levels IV and V\textsuperscript{22,26,27}—although Ramírez et al.\textsuperscript{22} did not clarify the GMFCS level, they included only non-ambulatory patients--; one study had patients with all GMFCS levels;\textsuperscript{25} and the remaining articles did not specify the GMFCS level. The predominant deformity is scoliosis. Treatments consisted of: traditional growing rods (3 articles), magnetic rods (1 article), early instrumented arthrodesis (2 articles), and one article each of the following: serial casting, DSB (dynamic spinal brace), DEFO (dynamic elastomeric fabric) orthosis, and vertical expandable prosthetic titanium ribs. The average follow-up was not indicated in two papers, the remaining eight have a mean follow-up range of 18 (1½ years) to 117.6 months (9.8 years). The variable that was repeated in all studies as important and allowed the comparison of outcomes was the Cobb angle, although Studer et al.\textsuperscript{29} did not specify the results of the Cobb angle in patients with CP and EOS. Some considered the growth of the thoracic or thoracolumbar spine as important variables (5 studies); others, the change in pelvic obliquity (4 studies), others considered the frontal and sagittal balances (2 articles) or used questionnaires to assess the outcomes (2 articles), and only one considered the rate of complications as an important variable.

**Surgical treatment**

The only articles that showed a correction of 75% or more of the Cobb angle were those that advocated early instrumented fusion;\textsuperscript{26,27} the use of traditional growing rods or titanium vertical expandable rib prostheses hardly exceeded 25% correction and did not exceed 50%;\textsuperscript{21,24,28} and serial plaster casting\textsuperscript{30} only managed to maintain the Cobb angle. DSB orthoses, however, stopped progression by 54%;\textsuperscript{23} but other less constrained orthoses only achieved 28%.\textsuperscript{25}

Among those that evaluated the improvement in height or spinal length,\textsuperscript{21,24,28,30} none reached 50% gain, the ones that achieved the best outcome were traditional growing rods.\textsuperscript{21} When considering the results of correction of pelvic obliquity,\textsuperscript{21,24,26,27} Eiffel Tower vertical expandable prosthetic titanium rib constructs were superior.\textsuperscript{24}

**Complications**

It is logical that non-surgical treatments show a much lower rate of complications (5.8-36%)\textsuperscript{23,30} than surgical ones (21.5-73.1%),\textsuperscript{21,22,26,27} and this is much higher in spastic children than in hypotonic children\textsuperscript{22} and in severe cases than in moderate ones.\textsuperscript{28} Type IIA and IIB surgical complications of the Smith et al.\textsuperscript{20} classification are the most frequent; although the spastic patients suffered all types of complications.\textsuperscript{22} Infections and problems related to the material are the most common complications in those operated on, and skin problems are more frequent when orthotic methods are used. The postoperative mortality rate associated with definitive fusion\textsuperscript{26} and the use of growing rods in spastic children\textsuperscript{22} is high.

**DISCUSSION**

It is evident that allowing an early-onset neuromuscular scoliosis to progress in patients with CP to very important values determines that future surgical treatments pose a greater risk and complexity. On the other hand, the quality of life of children operated due to EOS does not seem to depend so much on the type of implant or the number of surgeries, but rather on whether it is a neuromuscular scoliosis, the patient is non-ambulatory, and on the number of complications. This has revealed, then, that children with highly compromised spastic CP (GMFCS level V) are the ones at greatest risk of surgical treatments affecting their quality of life.

In addition, an especially important goal in children <5-6 years with EOS is to prevent an adverse change in the shape and function of the chest in order to achieve the most optimal development of lung function possible.\textsuperscript{15}
Neuromuscular Scoliosis

Previous studies

In the 21 systematic reviews, meta-analyses, and comparative studies, very young patients with spastic CP (<5-6 years) are not discriminated against, making it impossible to draw conclusions about this subgroup; only a few observations can be inferred.

Despite the rate of progression and the great possibilities of presenting very severe curves at the end of growth, with great respiratory compromise, at present, a single and superior treatment for EOS in patients with spastic CP has not been defined. These children often have serious concomitant medical problems (malnutrition, seizures, gastrostomies, tracheostomies, etc.).

Non-surgical treatments

Non-surgical options available to treat EOS in children <5-6 years old are: serial casting, orthoses, modifications in seating systems. Corrective casting has been useful in certain cases of EOS; it is generally indicated for curves between 30° and 50°-60° and for patients <4-5 years old. Unfortunately, information on CP patients treated with this method is scarce and inadequate. In addition, and although the type and rate of complications are low and minor, in general, the majority of those who use casting as treatment for EOS do not use it for the spastic CP subtype. It is believed that, in GMFCS level V quadriplegic patients, the difficulties and risks of its use would outweigh the benefits; the study by Lavalva et al. showed that they can be indicated especially in very young children (average 3.2 years), according to Mehta’s principles, with an acceptable level of curve control maintenance, until another type of treatment is used.

Orthoses are effective for curve control in spastic non-ambulatory patients, and are accepted along with modifications to seating systems as a means of conservative treatment in children with scoliosis and CP. Modifications to wheelchairs have some utility in controlling neuromuscular curves, but, in patients with CP, flexible braces are not effective in treating the deformity, and there is no strong evidence to advise their use in children with CP and scoliosis. Instead, a recent study on the use of bivalve orthoses confirmed their effectiveness for the maintenance and correction of the Cobb angle in a wide age range. In our current review, the DSB orthosis stopped progression by 54%, while the less constrained ones had much lower efficacy (28%).

Surgical treatment

Surgical treatments are based on the use of three different types of systems: distraction systems, compression systems and growth guidance systems. Growth guidance systems include traditional growing rods, vertical expandable prosthetic titanium ribs, magnetic growing rods, Shilla, Luqué trolley systems, sliding rods with sublaminar wiring, and mixed systems. In the literature, its usefulness in young children with CP and EOS is not very clear. Of the 10 studies analyzed here, it is possible to break down the average ages at the time of the treatments (Table): it should be noted that all the studies on surgical treatments included patients with an average age >5 years.

There is also no agreement regarding the general indications for surgical treatment; in some of them, they were based on the progression of the deformity and the deterioration of function and quality of life rather than objective radiographic parameters (Cobb angle, chest height, height of the lumbar or thoracic spine); others, however, were based on the value of the Cobb angle (>45°, >50°-60°, < or >90°), or on the preference of the surgeon.

Regarding the results of these techniques, Wijdicks et al. evaluated the growth potential of the different guidance systems, and observed that, despite the fact that most report T1-S1 growth similar to that indicated as normal by Dimeglio (1 cm/year), a large proportion of this growth depends on the corrections achieved with the initial and final surgeries, not actually during growth.

Interestingly, none of the articles evaluated analyzed in depth the improvement of lung function in operated patients; this is probably due to the low age of the patients (<5-6 years), because the lack of adequate collaboration invalidates functional tests, and also due to severe cognitive impairment. In any case, some indirectly evaluated said function by means of chest height or the space available for the lungs. Although, in the latter, an improvement in the parameters was demonstrated in all cases, the data were not conclusive.
On the other hand, although the trend towards anterior surgeries in EOS has decreased over the years, anterior spinal growth tethering, which spares the trunk muscles and maintains range of motion, still has defenders for the treatment of idiopathic EOS.40,41 Unfortunately, its effectiveness does not surpass or supplant orthoses42 and its use in EOS of neuromuscular etiology lacks bibliographic support.

Conservative treatment versus surgery

Interestingly, the study by Johnston et al.43 compared the use of serial plaster casting with growing rods and showed that, with the former, the deformity can be well controlled without compromising spinal growth and avoiding the high rate of complications in the rods placed in very young children.

Of the 10 studies, only Yaszay et al.27 used a quality-of-life assessment through the CPCHILD Index (Caregiver Priorities and Child Health Index of Life with Disabilities) given to caregivers before and after surgery, while, in non-surgical treatment, Nakamura et al.23 evaluated said quality using the Bridwell et al. questionnaire for scoliosis in flaccid neuromuscular diseases. Unfortunately, it was not possible to make reliable comparisons regarding the outcomes between both types of treatment (surgical vs. non-surgical).

Complications

The new surgical technologies that have emerged with the intention of improving outcomes and reducing complications continue to have a high burden of morbidity and mortality, complications, and unplanned secondary interventions, and a perioperative mortality rate of up to 18%.17 A study on vertical expandable titanium rib prostheses had an average of 2.1 complications per patient;44 neuromuscular scoliosis is particularly prone to them.45 Some authors frequently use rib distraction-based constructs for high tone patients46 and, although there do not seem to be differences in outcomes nor in complications compared to pure vertebral assemblies, the latter generally achieve a better correction than rib assemblies.47

The following complications are not uncommon: tears, disassembly, metallosis, mechanical failure of the magnetic growing rods, failure to prevent progression, infection, material prominence, neurological deficits, sagittal plane abnormalities and junctional kyphosis, ‘adding-on’ phenomenon, and the appearance of compensatory curves, premature spontaneous fusions, and negative psychological effects.22,48 In patients with neuromuscular scoliosis, the rate of unplanned surgeries due to complications with growing rods is usually high.49

In this review, it was clear and logical that the rate of complications was lower in non-surgical treatments (5.8-36%)23,30 than in surgical treatments (21.5-73.1%).21,22,24,26,27 It was much higher in spastic patients than in hypotonic patients22 and in severe cases than in moderate ones.28 The classification by Smith et al.20 showed that type IIA and IIB complications were the most frequent in the operated patients, but the spastic patients had all types of complications.22 As expected, infections and implant-related problems were the most common complications in those operated on, and skin problems were more frequent in those treated with orthopedic containment methods. However, the postoperative mortality rate associated with definitive arthrodesis26 and the use of growing rods in spastic children is striking.22 This latter study clearly shows a higher incidence of complications in patients with neuromuscular EOS with high muscle tone (spastic) –the object of this review– for a dual system of growing rods with tethering in ribs and pelvis.

Evaluation of the methodological quality of the studies and recommendations for future research

Although there are treatment algorithms to guide decisions in the management of EOS in general, there is a clear lack of data on the most appropriate and least risky treatment for the subset of young children with spinal deformity due to spastic CP.

Of the 10 studies selected and reviewed here, all should be considered for their type IV level of evidence,21-27,29 except that of Helenius et al.28 and that of LaValva et al.,30 which are level III.

Another problem is the way of communicating the results, which affects the possibilities of adequate comparison between different treatments. The systematic comparison of Wijdicks et al.39 regarding the growth potential of different guidance systems revealed another important problem in obtaining solid evidence: there is no unanimity in the way of communicating the remaining growth and, therefore, these reports are inadequate and do not allow a good comparison between the different techniques.
In addition, we saw here that the numbers of patients with spastic CP from the different studies are very varied, with the average ages ranging from 3.2 years to 10 years. A single trial included only patients with level V of the GMFCS; another three, only patients with level IV and V; and one trial included patients of all levels, while the rest did not specify the level.

Lastly, a point of conflict in these non-ambulatory patients is the relationship between the spine and the hips: many usually have subluxations or dislocations, which makes global treatment difficult. However, no evaluated study considers this relationship in terms of the concomitance of the deformities or the chronology of its correction, beyond what was analyzed regarding pelvic obliquity.

**CONCLUSIONS AND INFERRED THERAPEUTIC RECOMMENDATIONS**

Young children (<5-6 years) with global compromise spastic CP (GMFCS level V) and multi-disabled children who develop progressive neuromuscular EOS should be actively treated since its detection. This review does not allow us to conclude, in a categorical and indisputable way, which is the best therapy for this subgroup of patients, due to the scarce literature available and its low evidence. However, it appears that, despite a lower tolerance than in hypotonic patients, a good option for these children is to start with serial plaster casting under general anesthesia. If they are not tolerated, aggressive treatment with custom-made semi-rigid orthoses, combined with modifications to the sitting systems, can be used. In those over 5 years of age, it is more effective and balanced, in terms of risks and benefits, to proceed to surgical treatment when the curve cannot be stopped with the previous methods. Surgical methods that maintain growth (traditional growing rods, vertical expandable prosthetic titanium ribs, magnetic growing rods, Shilla technique, etc.) are not the best initial option given the high rate of complications in spastic children and very young children, but their efficacy and safety increase in those older than 5-6 years.

There is a clear trend to avoid early definitive fusion in high tone (spastic) neuromuscular patients.

In Figure 2, a personal algorithm is shown considering these observations.

However, randomized studies with a higher level of evidence, with strict selection based on the characteristics of these types of patients, are needed to adequately define the best treatment in this subgroup of patients.

![Figure 2. Therapeutic algorithm proposed according to the review carried out.](image-url)
REFERENCES


