Spinal muscular atrophy 5Q – Treatment with nusinersen

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Final version: *May 5, 2018*

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http://dx.doi.org/10.1590/1806-9282.64.06.484

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

The spinal muscular atrophy (SMA) is a neurodegenerative condition with autosomal recessive genetic inheritance. Nusinersen is an antisense oligonucleotide drug that modifies the SMN2 pre-mRNA processing to promote increased production of the full-length SMN protein. The purpose of this guideline is to provide recommendations that may assist in the decision-making regarding the use of nusinersen in patients with SMA 5q. For this, a systematic review of the literature was performed, without period restriction, in the Medline/PubMed, Central (Cochrane), and Lilacs databases via VHL, retrieving 243 papers, of which two randomized clinical trials were selected to respond to clinical doubt. The details about the methodology and the results are set out in Appendix I.

INTRODUCTION

The spinal muscular atrophy (SMA) is a neurodegenerative condition with autosomal recessive genetic inheritance. It is caused by a homozygous deletion of the survival motor neuron gene (SMN1). This genetic alteration results in a reduction of survival motor neuron (SMN) protein levels, leading to spinal cord alpha motor neurons degeneration, resulting in progressive symmetric proximal muscle weakness and paralysis[1,2]. Nusinersen is an antisense oligonucleotide drug that modifies the SMN2 pre-mRNA processing to promote increased production of the full-length SMN protein[3].

The incidence of SMA is often cited as approximately ten in every 100,000 live births. A recent review found estimates ranging from 5.0 to 24 per 100,000 births. The estimated prevalence is approximately one to two in 100,000 people[4].

SMA is diagnosed through genetic testing. An initial test evaluates the homozygous deletion of 5q in the survival motor neuron 1 (SMN1) gene, which identifies 95% of cases. If negative, the sequencing of the SMN1 gene is carried out as a second step. Nerve conduction studies and electromyography (EMG) are performed in a subgroup of patients. However, even when evidence of motor neuronopathy is identified in the study, a confirmatory genetic testing is carried out[5,6].

They are classified as type I (Werdnig-Hoffman disease), type II (Dubowitz disease), Type III (Kugelberg-Welander disease) and type IV (adult form). Type I is fatal in childhood, type II has a late onset during childhood and is associated with survival up to the second or third decade. Type III begins in childhood, is slowly progressive and comprises about 10% to 20% of all patients with SMA[7]. SMA type IV is the adult phenotype of SMA, characterized by mild muscle weakness usually beginning in the second or third decade of life. Infants with onset of symptoms during the prenatal period or within the first week of life are classified with SMA type 0, a very rare phenotype (<1%)[9].

SMA Type III: (also called juvenile SMA or Kugelberg-Welander disease), it appears after 18 months, but the age of onset varies greatly. According to Wirth et al.[8], the onset of the disease before 3 years of age is classified as SMA type IIIa, whereas, after this age, it is classified as SMA type IIIb. What differentiates both is the ability to walk, with individuals with type IIIa being able to walk up to the age of 20, while type IIIb patients of the same age never lose that ability[9]. Difficulties in swallowing, coughing, or nocturnal hypoventilation are less frequent than in type II patients, but they may occur. Over the years, these individuals may develop scoliosis. The life expectancy for these patients is undefined[10].

RESULTS

The Endear[3] study (Finkel, L. et al., 2017) assessed children who had genetic documentation of a homozygous deletion or mutation in the SMN1 gene; two copies of the SMN2 gene and, therefore, is considered more likely to develop type I SMA; onset of clinical symptoms compatible with spinal muscular atrophy at 6 months of age or younger; were 7 months of age or younger at screening and did not have low peripheral oxygen saturation (ie, did not require respiratory care). Exclusion criteria for this study were patients with hypoxemia, signs or symptoms of SMA present at birth or in the first week after birth, history or active condition that would interfere with lumbar puncture or study evaluation, and any history of gene therapy, prior antisense oligonucleotide (ASO) or cell transplantation.

Randomization was stratified according to the duration of the disease. The intervention was the intrathecal administration of nusinersen (nusinersen group) at an adjusted dose according to the estimated volume of cerebrospinal fluid for age, in such way that a patient of 2 years of age or more received the equivalent of a 12 mg dose (in a 5 ml solution), and younger children received smaller volumes, containing smaller doses of the drug. In the nusinersen group, doses were given on days 1, 15, 29 and 64, and maintenance doses on days 183 and 302 (maintenance dose every four months). A sham procedure[3] was used on the control group (**A**). **Table 1**

Prognostic differences in this study: patients treated with nusinersen at the beginning of the study had a higher percentage of paradoxical breathing (89% vs 66%), pneumonia or respiratory symptoms (35% vs 22%), difficulties in swallowing or feeding (51% vs 29%) and need of respiratory support (26% vs 15%) compared with patients in the sham group.

A pre-specified interim analysis was conducted by the sponsor and the data and safety monitoring board in which approximately 80 children were enrolled for at least six months. The analysis showed a benefit-risk assessment in favor of nusinersen. This result led to the early termination of the study. At that time, children were invited to undergo an end-of-study visit at least two weeks after receiving their most recent dose of nusinersen or having undergone their most recent dummy procedure.

By the end date of the final analysis, 39% of the nusinersen and 68% of the control group babies died or received permanent ventilatory support (event-free survival[c])[3] (**A**).

The composite outcome death OR permanent ventilatory support use had a likelihood of occurrence, at any point in time, 47% lower in the nusin-

TABLE 1 - BENEFIT AND/OR HARM - ABSOLUTE DATA

OUTCOME	N/NEC	N/NEI	ARC%	ARI%	IAR% (95%CI)	NNT	95%CI
HINE respondents Section 2 (6-month interim analysis)	27/0	51/21	0	41.2	41.2 (27.7 - 54.7)	2	2 - 4
Respondents CHOP INTEND [b]	37/1	73/52	3%	71%	68.5 (57 - 80)	1	1 - 2
Adverse events	41/40	80/77	97.6	96.3	1.3 -4.9 - 7.5	NS	

N: number of patients analyzed; NEI: number of events in intervention; **NEC**: number of events in control; ARI: absolute risk in intervention; **ARC**: absolute risk in comparison; **ARR**: absolute risk reduction; **IAR**: increase in absolute risk; **NNT**: Number needed to treat; **NNH**: number needed to harm; **CI:** confidence interval of 95%; **ITT**: analysis by intention to treat. (**a**) Respondent of Hine section 2 = According to the section 2 of the Hammersmith Infant Neurological Examination - Hine: an increase of ≥2 points [or maximum score] in the ability to kick, OR an increase ≥1 point in the motor control steps of the head, roll, sit, crawl, stand or walk, and improvements in more categories of motor stages than aggravations is defined as a respondent for this primary analysis. (**b**)Respondent of Chop Intend = percentage of patients with at least 4-point improvement over baseline in the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease - Chop Intend - whose scores range from 0 to 64, with the highest scores indicating better motor function. (**c**) Event-free survival = Event-free survival, which was defined as the time up to death or use of permanent assisted ventilation (tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days, in the absence of an acute reversible event).

ersen-treated group (Hazard Ratio (HR) =0.53; 95% Confidence Interval [CI], 0.32-0.89, p=0.005). This benefit was higher among patients included in the study with disease duration ≤13.1 months, compared with those with >13.1 months[3] **(A)**.

The median time until death or use of permanent ventilatory support was 22.6 weeks in the control group and was not achieved in the nusinersen group[3] **(A)**.

When results were separated for each type of outcome (death and permanent ventilatory support), the results indicated a statistically significant difference between the nusinersen group and the simulated procedure in overall survival (HR=0.37, 95%CI 0.18 to 0 , 77), but not for permanent ventilatory support (HR=0.66, 95%CI 0.32 to 1.37). It is possible, however, that due to loss of data caused by the premature termination of the study, as well as a shorter duration of follow-up, the statistical power has been reduced[3] **(A)**.

A smaller percentage of infants in the nusinersen group than in the control group died at the end of the study (16% vs 39%). The death outcome had a likelihood of occurrence, at any point in time, 63% lower in the nusinersen-treated group (HR=0.37; 95%CI, 0.18 to 0.77; p=0.004). There was no difference between groups in the likelihood of using permanent ventilatory support at any point in time (HR=0.66 95% CI (0.32-1.37); p=0.13); 23% of the children in the nusinersen group and 32% in the control group received permanent ventilatory support)[3] **(A)**.

RECOMMENDATION

In children with a diagnosis of SMA type I, the use of intrathecal nusinersen with a dose adjusted according to the estimated volume of cerebrospinal fluid by age (equivalent to a dose of 12 mg for a 2-year-old patient) given on days 1, 15, 29 and 64 and maintenance doses on days 183 and 302 (maintenance doses every four months), compared to a simulated treatment, in up to six months:

- Increases the number of "respondent" patients (with improved motor function) by 41.2%, being necessary to treat two patients so that one was "respondent" (NNT = 2) - analysis with Hine section 2. Study power for bilateral 95% IC is 98%. In an intention-to-treat analysis (ITT), the number of "respondents" increased by 26%, 95%CI 17 to 36; being necessary to treat four patients for every "respondent" (NNT = 4, 95%CI 3 to 6), with a study power for bilateral 95%CI of 95.7%. **(A)** **(Table 1)**
- The outcome death OR permanent ventilatory support use (composite outcome) had a likelihood of occurrence, at any point in time, 47% lower in the nusinersen-treated group. This benefit was higher among patients with disease duration ≤13.1 months. **(A)**
- The death outcome had a likelihood of occurrence, at any point in time, 63% lower in the nusinersen-treated group. **(A)**
- There is no difference between groups in the likelihood of using permanent ventilatory support at any point in time. **(A)**
- The proportion of patients who achieve an improvement of 4 or more points ("respondents") increases by 68% in the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease - Chop Intend, whose scores range from 0 to 64, and higher scores indicate better motor function (NNT = 1). Study power for bilateral 95% IC is 100%. **(A)** **(Table 1)**
- There is no difference in the number of treatment-related adverse events between both groups. **(A)**

The Cherish[11] (Mercuri, E. et al., 2018) randomized phase III study, sham-controlled, included patients (N=126) with symptoms compatible with SMA type II and age between 2 and 12 years (84% of patients at baseline were under 6 years of age)[11](A). Patients presented genetic documentation of deletion of the homozygous 5q SMA gene, homozygous or composite heterozygous mutation, and beginning of clinical signs and SMA-compatible symptoms after 6 months of age. They could sit independently but never had the ability to walk independently. They had a Hammersmith Functional Motor Scale-Expanded (HFMSE) score for motor function of ≥10 and ≤54 at screening (HFMSE scores range from 0 to 66, with higher scores indicating better motor function). The following exclusion criteria were considered: respiratory failure, gastroenteric tube feeding, severe scoliosis and contractures, history or active condition that would interfere with lumbar puncture, treatment with another experimental drug, treatment with valproate or hydroxyurea in the last three months, any history of gene therapy, antisense oligonucleotide therapy, or cell transplantation.

The intervention group (n=84) received 12 mg (in a 5 mL solution) of nusinersen administered intrathecally on days 1, 29, 85 and 274 (maintenance dose every six months) and the control group (n=42), a simulated procedure (sham group)[11] **(A)**.

Prognostic differences in this study: an imbalance in the proportion of patients who had been able to stand up unsupported (13% of patients in the nusinergen group, 29% in the sham control group) or walk with support (24% of patients in the nusinergen group and 33% in the control group).

The Cherish study was prematurely terminated due to ethical reasons arising out of the positive results generated from an interim analysis.

The interim analysis of the primary outcome was performed when all the children had been enrolled for at least six months, and at least 39 children completed the evaluation of 15 months. The analysis was performed with the use of a multiple imputation method. The number of children with data observed for the 15-month evaluation was 35 in the nusinersen group and 19 in the control group, and the number of children with imputed data was 49 in the nusinersen group and 23 in the control group. In the final analysis, the following outcomes were analyzed using a multiple imputation method: baseline change in the HFMSE score, percentage of children with a change in HFMSE score of at least 3 points, and baseline change in the Revised Upper Limb Module (Rulm) ranging from 0 to 37, with higher scores indicating better motor function. The percentage of children who achieved at least one new World Health Organization (WHO) milestone (out of a total of six milestones) was also assessed.

Only children with observed data were included in the other analyzes. The number of children with data observed for the 15-month evaluation was 66 in the nusinersen group and 34 in the control group, and the number of children with imputed data was 18 in the nusinersen group and 8 in the control group[11](A).

There was improvement in motor function (HFMSE score) from the start of the study in nusinersen-treated patients compared to control patients (difference in minimum mean square points, 5.9 (3.7 to 8.1); p <0.0001). HFMSE scores range from 0 to 66, with higher scores indicating better motor function[11](**A**). (**Table 2**)

There was an improvement in motor function from the baseline in the Rulm score (ranging from 0 to 37, with higher scores indicating better motor function) with the use of nusinersen in comparison with the control group (difference of minimum mean square points 3.7 (2.3 to 5.0), p <0.0001)[11](**A**). (**Table 2**)

A higher percentage of children in the nusinersen group compared to the control one had a baseline increase, at month 15 in the HFMSE score, of at least 3 points (57% vs 26%, P <0.001)[11](**A**).

The percentage of children who achieved at least one new WHO milestone did not differ significantly between the nusinersen group and the sham group (20% [95% CI 11 to 31] and 6% [CI 95% 1 to 20], respectively; 14% ratio difference [-7 to 34], p=0.08)[11](**A**).

The overall incidence of adverse events was similar in the nusinersen and control groups (93% and 100%, respectively), as well as the incidence of moderate or severe adverse events[11](**A**).

RECOMMENDATION

In children with a diagnosis of SMA type II, the use of intrathecal nusinersen at a 12 mg dose (in a 5 ml solution) administered on days 1, 29, 85 and 274 (maintenance dose every six months), in up to 15 months:

- Improves motor function (HFMSE score) - difference in minimum mean square points = 5.9 (3.7 to 8.1), p<0.0001). HFMSE scores range from 0 to 66, with higher scores indicating better motor function. (**A**)
- Increases baseline HFMSE score in at least 3 points (HFMSE scores range from 0 to 66, with higher scores indicating better motor function), (57% vs 26%, p<0.001). (**A**)
- There is no difference in the percentage of children who achieved at least one new WHO milestone, out of a total of six milestones. (**A**)
- Improves motor function from the baseline in the Rulm score (ranging from 0 to 37, with higher scores indicating better motor function) - dif-

TABLE 2 - BENEFIT AND/OR HARM - AT 15 MONTHS

OUTCOME	INTERVENTION (N = 84) Minimum mean Square (95% CI)	COMPARISON (N = 42) Minimum mean Square (95% CI)	Difference (95% CI)	p
Baseline change in HFMSE score	4.0 (2.9 to 5.1)	-1.9 (-3.8 to 0.0)	5.9 (3.7 to 8.1)	< 0.0001
Baseline change in Rulm score	4.2 (3.4 to 5.0)	0.5 (-0.6 to 1.6)	3.7 (2.3 to 5.0)	< 0.0001

ference of minimum mean square points = 3.7 (2.3 to 5.0), p<0.0001). **(A)**

- There is no difference in the number of adverse events. **(A)**

DISCUSSION

Two phase III clinical trials were included in this guideline. The first trial (Finkel, R.S. Et al., 2017)[3] assessed the use of intrathecal (IT) nusinersen with a dose adjusted according to the estimated volume of cerebrospinal fluid by age (equivalent to a dose of 12 mg for a 2-year-old patient) given on days 1, 15, 29 and 64 and maintenance doses on days 183 and 302, in SMA type I patients compared to a sham treatment. There was a reduction in the risk of death or use of permanent ventilatory support (47% lower in the nusinersen group than in the control group). However, when results were separated for each type of outcome (death and permanent ventilatory support), the results indicated a statistically significant difference between the nusinersen group and the simulated procedure in overall survival (risk of death) with HR=0.37 and 95%CI 0.18 to 0 , 77, but not for permanent ventilatory support (HR=0.66, 95%CI 0.32 to 1.37). It is possible, however, that due to loss of data caused by the premature termination of the study, as well as a shorter duration of follow-up, the statistical power has been reduced. IT nusinersen proved to be safe, with no difference in the number of treatment-related adverse events between both groups.

A second clinical trial phase III (Mercuri, E. et al., 2018)[11], not included in the Canadian Agency for Drugs and Technologies in Health (CADTH) technology assessment because of the use of a treatment regimen or dose https://www.cadth.ca/sites/default/files/cdr/clinical/SR0525_Spinraza_CL_Report.pdf), assessed the use of IT nusinersen in patients with SMA type II.

In this study, the dose of IT nusinersen was 12 mg (in a solution of 5 mL), administered on days 1, 29, 85 and 274. There was an improvement in motor function (HFMSE score) from the start of the study in patients treated with nusinersen compared to control patients (minimum mean square difference, p<0.0001), but there was no difference between the percentage of children reaching at least one new WHO milestone, out of a total of six milestones.

Aiming at presenting health professionals with guidelines to enable them to provide the best care and the most advanced technologies, the UK government created The National Institute for Clinical Excellence (Nice) in 1999. To date, Nice has not published guidelines for the use of IT nusinersen in patients with 5q SMA. However, there is a scheduled date for publication (November 21, 2018; https://www.nice.org.uk/guidance/indevelopment/gid-ta10281).

In Brazil there are no therapeutic guidelines on the use of IT nusinersen for SMA 5q published at the moment (April 29, 2018) by the National Commission for the Incorporation of Technology in SUS (Conitec; http://conitec.gov.br/), although the drug is registered under Anvisa (http://portal.anvisa.gov.br/).

APPENDIX I

Clinical question

In children with spinal muscular atrophy (SMA) 5q, is the use of nusinersen effective and safe?

Eligibility criteria

The main reasons for exclusion were: they did not respond to the PICO and study design.

Only studies with a randomized controlled clinical trial (RCT) design were included.

Search for papers

Database

The scientific information databases consulted were Medline/PubMed, Central (Cochrane) and Lilacs via VHL.

Identification of descriptors

P	Spinal muscular atrophy
I	Nusinersen
C	Sham procedure or conventional therapy
O	Clinical outcomes

Research strategy

Medline/PubMed: (Spinal Muscular Atrophies of Childhood OR Muscular Atrophy, Spinal) AND (nusinersen OR Oligonucleotides, Antisense)

Central (Cochrane): (Spinal Muscular Atrophy OR Spinal Muscular Atrophy) AND nusinersen

Lilacs via VHL: (Spinal Muscular Atrophy OR Spinal Muscular Atrophy) AND nusinersen

Critical evaluation

Relevance - clinical importance

This guideline was prepared by means of a clinically relevant question in order to gather information in medicine to standardize approaches and assist in decision-making.

Reliability - Internal validity

The selection of the studies and the evaluation of the titles and abstracts obtained from the search strategy in the databases consulted were independently and blindly conducted, in total accordance with the inclusion and exclusion criteria. Finally, the studies with potential relevance were separated.

When the title and the summary were not enlightening, we sought for the full article.

Only studies with texts available in its entirety were considered for critical evaluation.

No restriction was made regarding the year of publication.

Languages: Portuguese, English, and Spanish.

Results application - External validity

The level of scientific evidence was classified by type of study, according to Oxford[12](Table 3).

TABLE 3 - RECOMMENDATION DEGREE AND EVIDENCE STRENGTH

A: Experimental or observational studies of higher consistency.
B: Experimental or observational studies of lower consistency.
C: Uncontrolled case/study reports.
D: Opinion deprived of critical evaluation, based on consensus, physiological studies or animal models.

The selected evidence was defined as a randomized controlled clinical trial (RCT) and submitted to an appropriate critical evaluation checklist (Table 4). The critical evaluation of RCT allows to classify it according to the Jadad score[13], considering Jadad trials <3 as inconsistent (grade B) and those with score ≥3 consistent (grade A).

TABLE 4 - GUIDE FOR CRITICAL EVALUATION OF RANDOMIZED CONTROLLED TRIALS

Study data Reference, study design, Jadad, level of evidence	**Sample size calculation** Estimated differences, power, significance level, total number of patients
Patient selection Inclusion and exclusion criteria	**Patients** Recruited, randomized, prognostic differences
Randomization Description and blinded allocation	**Patient follow-up** Time, losses, migration
Treatment protocol Intervention, control, and blinding	**Analysis** Intention to treat, analyzed intervention and control
Outcomes considered Primary, secondary, measurement instrument for the outcome of interest	**Results** Benefits or harmful effects in absolute data, benefits or harmful effects on average

During the critical evaluation, the Grade[15] (Grading of Recommendations Assessment, Development and Evaluation) discriminatory instrument was applied, using evidence of high and moderate quality. (Tables 5, 6 and 7)

The risks of bias identified in the studies selected were an early termination of the study due to benefits and different patients regarding previously known prognostic factors (common to both RCTs). The other parameters assessed for risk of bias were adequate in both RCTs (Tables 5, 6 and 7).

Method of extraction and result analysis

For results with available evidence, the population, intervention, outcomes, presence or absence of benefits and/or harmful events, and controversy must be specifically defined whenever possible.

The results will be presented preferably in ab-

TABLE 5 - RISK OF BIAS IN INCLUDED RCTS (GRADE[14])

Parameters evaluated	Finkel RS[3]	Mercuri E[11]
Adequate randomization?	Yes	Yes
Was the allocation blinded?	Yes	Yes
Were the patients analyzed in the groups for which they were randomized (was there IT analysis)?	Yes	Yes
Were the patients in the groups similar in previously known prognostic factors?	No	No
Was the study blinded?	Yes	Yes
Except for experimental intervention, were the groups treated equally?	Yes	Yes
Were the losses significant?	Early termination and ITT	Early termination and ITT
Was there an early termination of study due to benefits?	Yes	Yes
Did the study have an accurate estimate of the effects of the treatment?	Yes	Yes
Are the study patients similar to those of interest?	Yes	Yes
Are study outcomes clinically relevant?	Yes	Yes
Have potential conflicts of interest been declared?	Yes	Yes

ITT = intention-to-treat analysis

TABLE 6 - CRITICAL EVALUATION WITH THE GRADE[14] DISCRIMINATORY INSTRUMENT (FINKEL, R.S. ET AL., 2017[3] STUDY - SMA TYPE I)

Certainty assessment							Nº of patients		Effect	Certainty	Importance
Nº of studies	Design of the study	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Intrathecal nusinersen	Sham	Absolute Risk (95% CI)		
Hine section 2 respondents (improved motor function) (follow-up: six months variation to; assessed with: Hammersmith Infant Neurological Examination - Hine section 2)											
Finkel RS[3]	randomized clinical trial	not serious[a,b]	not serious[c]	not serious	not serious	None	21/51 (41.2%)	0/27 (0.0%)	41.2% (27.7 - 54.7)	HIGH	CRITICAL

CI = confidence interval. Explanations. a. Early termination. b. Patients differ in previously known prognostic factors. c. not valuable

TABLE 7 - CRITICAL EVALUATION WITH THE GRADE[15] DISCRIMINATORY INSTRUMENT (MERCURI, E. ET AL., 2017[11] STUDY - SMA TYPE II)

Certainty assessment						
Study	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence
Mercuri E[11]	not serious [a,b]	serious[c]	not serious	not serious	None	MODERATE

Explanations: a. Early termination due to benefits . b. Patients with different prognostic factors at the beginning of the study, between the groups. c. There was an improvement of the motor function in the HFMSE and Rulm analyses with nusinersen. However, there was no difference in new WHO milestones.

solute data, absolute risk, number needed to treat (NNT) or number needed to harm (NNH) and, eventually, in mean and standard deviation values (Table 8).

TABLE 8 - WORKSHEET USED FOR DESCRIBING AND PRESENTING THE RESULTS FOR EACH STUDY

Evidence included
Study design
Selected population
Follow-up time
Outcomes considered
Expression of results: percentage, risk, odds, hazard ratio, mean

RESULTS

Studies returned (05/2018)

TABLE 9 - NUMBER OF PAPERS RETURNED FROM THE SEARCH METHODOLOGY USED IN EACH OF THE SCIENTIFIC DATABASES

DATABASE	NUMBER OF PAPERS
Primary	
PubMed-Medline	188
Central (Cochrane)	10
Lilacs via VHL	45

TABLE 10 - NUMBER OF PAPERS SELECTED

Type of publication	No. of papers	Included	Excluded
Randomized trial	2	2	0

Application of evidence - Recommendation

The recommendations will be elaborated by the authors of the review, with the initial characteristic of the synthesis of evidence, being subject to validation by all authors who participated in creating the guideline.

The available evidence will follow some principles of exposure: it will be by outcome and will have as components: number of patients, type of comparison, magnitude, and precision (standard deviation and 95% CI).

Its strength will be estimated (Oxford[12]/Grade[15]) as 1b and 1c (grade A) or strong, and as 2a, 2b and 2c (grade B) or moderate , weak, or very weak.

Conflict of interest

There is no conflict of interest related to this review that can be declared by any of the authors.

Final declaration

The Guidelines Project, an initiative of the Brazilian Medical Association in partnership with the Specialty Societies, aims to reconcile medical information in order to standardize approaches that can aid the physician's reasoning and decision-making process. The information contained in this project must be submitted to the evaluation and criticism of the physician responsible for the conduct to be followed, given the reality and clinical condition of each patient.

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