CLINICAL-PRACTICE GUIDELINES FOR THE PREVENTION, DIAGNOSIS AND TREATMENT OF RETINOPATHY OF PREMATURITY (ROP)*

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KEY TO ABBREVIATIONS

AAs	Aminoacids
AGREE	Appraisal of Guidelines for Research and Evaluation
AP-ROP	Aggressive Posterior ROP
BIO	Binocular indirect ophthalmoscope
BOOST	Benefits of Oxygen-Saturation Targeting *(Oxygen saturation and outcomes in preterm infants)*
BPD	Bronchopulmonary dysplasia
BW	Birth weight
CAO	Argentine Ophthalmology Council
CEFEN	Committee on Fetal-Neonatal Studies, Argentine Society of Pediatrics
COT	Canadian oxygen trial *(Oxygen saturation and outcomes in preterm infants)*
CPAP	Continuous positive airway pressure
CPD	Chronic pulmonary disease
CPG	Clinical-practice guidelines
CQ	Clinical question
CR	Crossed risk
CRYO ROP	Cryotherapy for Retinopathy of Prematurity
DR	Differential risk
EPO	Erythropoietin
ETROP	Early Treatment for the Retinopathy of Prematurity

EUGR	Extrauterine-growth restriction
FiO_2	Fraction of inspired oxygen
GA	Gestational age
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAI	Hospital-acquired/nosocomial infection
HDSR	Recommendations with high degree of evidence and strength
HM	Human milk
HMD	Hyaline-membrane disease
HSV	Herpes-simplex virus
ICROP	International Classification of Retinopathy of Prematurity
IGF	Insulin-like growth factor
IGFBP3	Insulin-like-growth-factor–binding protein 3
ITT	Interdisciplinary Technical Team
IUGR	Intrauterine-growth restriction
IVH	Intraventricular hemorrhage
MAP	Mean airway pressure
MO	Missed opportunity
NB	Newborn
NEC	Necrotizing enterocolitis
NeOProM	Neonatal oxygenation prospective meta-analysis
NICU	Neonatal-intensive-care unit
NIDCAP	Neonatal Individual Developmental Care and Assessment Program
95% CI	95% confidence interval

NNT	Number necessary for treatment
O2	Oxygen
p	Probability of finding a result equal to, or more extreme, than that actually observed
PaO_2	Arterial oxygen pressure
PDA	Patent ductus arteriosus
PEEP	Positive end-expiratory pressure
PICoR	Scheme *Patient-Problem—>Intervention—>Comparison—>Result* for carrying out PC (Patient Care)
PIPP	Premature-infant–pain profile
PMA	Postmenstrual age
PPV	Positive-pressure ventilation
PUFA	Polyunsaturated fatty acid
RCT	Randomized clinical trial
RCnT	Randomized controlled trial
RD	Retinal detachment
RDS	Respiratory-distress síndrome
RFs vs. PFs	Risk vs. protection factors
ROP	Retinopathy of prematurity
RR	Relative risk and Respiratory rate
SAOI	Argentine Society of Infantile Ophthalmology
SAP	Argentine Pediatric Society
SIGN	Network for evaluating the quality of a systematic review (*Scottish Intercollegiate Guidelines Network)*
SR	Systematic review

STOP ROP	Study on supplementary oxygen therapy for retinopathy of prematurity *(Supplemental therapeutic oxygen for retinopathy of prematurity)*
SUPPORT	Surfactant, Positive Pressure, and Oxygenation Randomized Trial *(Study of NICHD- Neonatal Research Network)*
UCs	Unusual cases
UK	United Kingdom
UNICEF	United Nations Children's Fund (formerly United Nations International Children's Emergency Fund)
USA	The United States of America
VLBW	Very low birthweight
WINROP	To evaluate the ability of a postnatal weight-gain algorithm (WINROP) to identify sight-threatening retinopathy of prematurity (ROP type 1) in a nation-based extremely preterm infant cohort.

INTRODUCTION

The problem

Retinopathy of prematurity (ROP) is a disease of the eye caused by a defect in the vascularization of the retina, which can alter normal retinal development and produce either a partial or a total loss of vision. ROP is the principal cause of blindness in infancy in both the middle- and the middle-to-high–income countries, such as Argentina.

ROP affects only preterm infants and especially those of birthweight (BW) 1,500 g or less and/or of fewer than 32 weeks of gestational age (GA). Nevertheless, the disease can also occur in preterm of greater BW and GA, denoted *unusual cases* (UCs). ROP can also be found in cases involving a complicated neonatal evolution as a result of risk factors—such as, for example, an inadequately controlled administration of oxygen (O_2), a lack of pulmonary maturation as a result of no prenatal steroids, intrauterine-growth restriction (IUGR), postnatal undernutrition, sepsis, and blood transfusions.

ROP can be prevented, in the majority of the cases, by the interventions practiced in those Neonatal-Intensive-Care Units (NICUs) that possess an adequate infrastructure and sufficient trained personnel to undertake the appropriate perinatal measures and control the aforementioned risk factors (the phase of *primary prevention*). An ophthalmological diagnosis at the appropriate moment through a systematic screening along with an opportune treatment serve to improve the prognosis for the vision of infants with the diagnosis of ROP (the phase of *secondary prevention*). Finally, those children who are cured, but with sequelae (*i. e.*, impaired vision or some degree of blindness) should be placed early on in programs of rehabilitation that will facilitate their eventual integration into and role in society (the phase of *tertiary prevention*).[1]

Natural development of the disease

The severity of the development of ROP is inversely related to the BW and the GA of the preterm babies and directly related to the presence of risk factors. Without prevention, opportune diagnosis, and adequate treatment, the disease presents three possible developments: a spontaneous remission along with an absence of signs or symptoms; a decrease in visual acuity from retinal scars, as diagnosed in ophthalmological controls during childhood; and blindness or serious visual impairment upon partial or total detachment of the retina.

Epidemiology

Retinopathy of prematurity, originally termed retrolental fibroplasia, was first described by Terry in 1942[2] and in the following decade was found to be responsible for 50% of infantile blindness in the United States and western Europe, an incidence that gave rise to the reference to that particular period as the "first epidemic of ROP". The BWs of the affected children fell within the range of 1,000 to 1,800 g. Smaller premature, however, did not survive during the '40s.

In 1951, Campbell[3] identified the role of the uncontrolled administration of O_2 as the principal risk factor for ROP, and accordingly, drastic measures were undertaken to decrease O_2 usage. This precaution significantly reduced the incidence of infant blindness through ROP, though the change increased the number of neonatal mortalities.

In the decades of the '70s through the '90s, as a result of the increase in neonatal survival in the developed countries, a so-called "second ROP epidemic" occurred, characterized by the presentation of smaller and more immature infants along with an initial reduction and final disappearance of cases in larger and more mature premature (UCs).[4]

The quality of care in the neonatal intensive-care units (NICUs) in combination with the competent programs of screening and treatments found in those countries, has allowed that children with severe ROP have an average of BW 700 g and reduced the GA to 25 weeks, has made the treatment of only 1 to 3% of those of BW less than 1,500 g necessary, and has caused ROP to be the reason for infant blindness in only 5 to 15% of the cases.[5]

Entirely different is the present situation in the developing countries or those of middle- to upper-middle average incomes—such as the Latin-American (including Argentina), the Asian, and the eastern-European nations—where neonatal survival has begun to increase thanks to the implementation of intensive-care services, although the diverse quality of the programs has provided only insufficient screening and delayed treatments. This circumstance has resulted in a rise in the cases of ROP in infants with BWs and GAs that are higher than those respective statistics in the developed countries along with the occurrence of UCs and those of unavailed opportunities in ROP treatment such that ROP has become the cause of infant blindness in up to 60% of the cases in neonates. This turn of events has accordingly become labelled the "Third Epidemic of ROP".[6]

Literature references for the Introduction Section

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SCOPE OF THE GUIDELINES

Proposal and general objective of the guidelines

The general proposal of these clinical-practice guidelines (CPGs) is to offer information based on the best available evidence in order to contribute to and improvement of the safety and the quality of medical care in the NICUs by strengthening both the managerial and the clinical decisions regarding the practices of prevention, diagnosis, and treatment of retinopathy of prematurity in our country with the end objective of definitively reducing the incidence of the disease through a more appropriate prevention of the risk factors and a standardization of the practices of diagnosis, treatment, and opportune referral to centers of visual rehabilitation and/or special education.

Over the long term, the guidelines manual is aimed at contributing to an improvement in the quality of life for the premature NBs by reducing the probability of impaired vision or blindness in their future childhood. Accordingly, the general objective of the manual is to detail recommendations based on high-quality evidence for the prevention, diagnosis, and treatment of ROP in those preterm NBs.

Specific objectives of the guidelines

These guidelines seek to generate recommendations for:

(1) identifying in preterm NBs during their stay in the NICUs, with an aim at prevention, the risk factors recognized as causal agents or potential aggravators of ROP based on clinical findings or other information obtained through complementary methods;

(2) contributing to a systematization and refinement of the methods of screening for ROP through the definition and application of objective criteria that will distinguish between a favorable or unfavorable development;

(3) stop or minimizing unfavorable developments on the basis of the efficacy, efficiency, and safety of therapeutic interventions proposed; and

(4) unifying criteria for the opportune referral of NBs preterm for visual sequelae for their rapid rehabilitation.

Target patient population

The patient population aimed at in this compendium of guidelines consists of:

(a) preterm NBs of fewer than 32 weeks GA and/or less than 1,500 g BW;

(b) preterm NBs with GAs from 33 through 36 weeks, having required O_2 or presented other risk factors for ROP at any time from birth to discharge from the hospital.

Target user population

The guidelines contained in this manual are directed principally, but not exclusively, at medical professionals who attend preterm NBs—including medical neonatologists; pediatricians; anesthesiologists; surgeons; ophthalmologists; nurses; health administrators; other public members in the ministries of health and in health insurance; directors of hospitals, clinics, and sanatoriums; parents of prematures; and specialist educators of children with impaired vision or blindness.

Expected health benefits

The availability of a manual of CPGs adequate for the prevention, diagnosis, treatment, and follow-up of ROP along with rehabilitation from the disease that is based on the most recent national and international scientific evidence will benefit at once the health-team professionals who attend preterm NBs, those infants themselves, their family, the educators, the entire community, and the State.

The guidelines for the health-team professionals are aimed at their fundamental orientation first in the prevention and then in the correct management of the pathology and its sequelae as well as in the adequate utilization of the available health resources; but the guidelines will also benefit the children, their family group, the educators, the community, and the State by facilitating a more consistent and comprehensive care of higher quality that is in accordance with international standards and that will minimize the possibility of a serious handicap such as impaired vision or blindness.

GENERAL METHODOLOGY

This CPG was formulated through a process whereby high-quality international guidelines were incorporated according to the criteria established by the National Ministry of Health's publication *Guide for the Adaptation of Clinical-practice Guidelines*[i] The methodology originally proposed was designed on the basis of specific tools created by agencies and national and international organizations and subsequently validated through experiments previously conducted in our country.[ii,iii,iv]

The writing of these guidelines was reviewed and brought up to date with an aim at augmenting the level of adherence to the standards for the production of guidelines proposed by the international network of clinical-practice guidelines (Guidelines International Network [GIN]) in 2012.[v] For the confirmation of the quality of the evidence, the methodologies of AGREE II, SIGN, and GRADE[vi] were used.

The evidence for the adaptation of the principles and practices for the diagnosis and treatment of ROP proposed in the present *Guidelines* was extracted from the *Guideline for the Screening and Treatment of Retinopathy of Prematurity* published by the British Royal College in May of 2008 [x].

In general, evidence from primary studies was not considered with the exception of two clinical questions (CQs) regarded of priority by the Interdisciplinary Technical Team (ITT) in which a process of *de-novo* formulation was implemented based on a systematic literature search of randomized controlled clinical trials (RCnTs).

The steps in the adaptation from the clinical-practice guidelines (CPGs) of the Royal College are detailed in the following section.

Formation and composition of the ITT

The ITT comprised premier authorities on the subject of ROP, experts in the related methodologies, and medical professionals who would be potential users of the Argentine CPG . The different members of the team are listed at the beginning of this summary.

Definition of the problem

The ITT defined the pathology and described the epidemiology, the clinical development, and the current status of the attention to the disease in Argentina.

Definition of the scope of the CPG

The ETI defined the scope of the CPG through a description of the general goal and specific objectives, the delimitation of the target population, the potential users along with the aspects of the attention and finally an estimation of the expected healthcare benefits.

Formulation of the CQs

Every CQ was formulated according to the scheme *Patient-Problem—>Intervention—>Comparison—>Result* (PICoR)

Guidelines for Clinical Practice: search and selection

The search for guidelines was carried out through the methodology of searching for the components of a good screening and treatment service: generic databases and reports of *meta*-analyses. In all instances the strategy was applied of searching specifically for each component on the basis of a series of pre-established criteria for inclusion and exclusion.

The CPGs were selected on the basis of pertinence (*i. e.*, the degree of concordance between the contents and the CQs formulated) and quality. The pertinence was evaluated by means of an *ad-hoc* tool that deliberated on six different domains—the CPG's objective, the day-to-day patients, the ambit of the medical attention, the routine professionals in attendance, the standard interventions under consideration (*i. e.*, prevention, diagnosis, treatment, rehabilitation), and the expected results—and then employed an evaluation scale of 0 to 2 (0, not pertinent; 1, pertinent; and 2, very pertinent). The CPGs with scores higher than 6, were considered for the step of quality evaluation. The quality was evaluated by means of the AGREE II (Appraisal of Guidelines for Research and Evaluation) [viii]. The quality of each CPG was assessed independently by two members of the ITT methodology squad, whose evaluation was expressed in the form of degrees of agreement or disagreement with respect to 23 items arranged within 6 different domains. To that end, each of the two evaluators applied a scale of 1 to 7 to each item; with 1–2 = in great disagreement, 3–4 = in disagreement, 5–6, in agreement, and 7 = in great agreement.

The standard scorings for each domain were estimated according to the methodology established by the AGREE Collaboration. According to the standard scores for each domain, the CPG evaluated was classified as:

highly recommendable at ≥60% in at least 4 domains,
recommendable at >30% and <60% in at least 4 domains,
not recommendable at ≤30% in at least 4 domains.

A standard score of ≤60% in the domain methodologic rigor was considered as a criterion for exclusion since that score is the one that guarantees the internal validity of the recommendations for the CPG.

The search carried out in the different databases yielded a total of 29 eligible publications of CPGs, of which group 5 complied with the criteria for inclusion. The guidelines in all those 5 were considered pertinent, but only 1 was evaluated as extremely recommendable and was thus employed as an input for the process of adaptation—namely the *Guideline for the Screening and Treatment of Retinopathy of Prematurity*, produced by the British Association of Perinatal Medicine of the Royal College of Pediatrics and Child Health of the United Kingdom, with a target population of neonatologists and ophthalmologists, and last revised in 2008.

Systematic reviews: search and selection

The search for systematic reviews (SRs) was aimed at evaluating the degree of up-to-datedness of the recommendations contained in the CPG under consideration and then incorporating any recent evidence that could contribute to a resolution of the CQs posed by the ITT. This search was performed with the databases Cochrane Library (previously known as the Cochrane Collaboration)—a nonprofit nongovernmental organization consisting in a group of more than 37,000 volunteers in more than 130 countries—(entitled *Database of Abstracts of Reviews of Effects), Literatura Latinoamericana y del Caribe en Ciencias de la Salud* (LILACS), of Pubmed, and of the Tripdatabase. All of those searches were executed through a strategy tailored specifically for each database and taking place between September of 2012 and August of 2014.

Criteria of eligibility, inclusion and exclusion were defined in order to be able to identify SRs that were potentially relevant to the topics of the CPG for incorporation.

The search performed in the different sources of data yielded a total of 533 SRs, of which group 276 duplications were eliminated. Of the remaining 257, 171 were considered eligible. Of this final number, 118 complied with the criteria for inclusion.

The pertinence of the SRs was evaluated by means of an *ad-hoc* tool in which a given SR was assessed independently by the two reviewers with respect to the relevance of the SR in question to the CQs posed by the ITT (*i. e.*, the pertinence matrix). The SRs resulting in a disagreement between those two reviewers were further evaluated by a third referee. In all instances, those SRs that provided information relative to a clarification of at least one CQ were kept under consideration.

The quality of each SR was evaluated through a tool created by the *Scottish Intercollegiate Guidelines Network* (SIGN) and as such was assessed by a single member of the ITT with an aim at verifying the methodology. A database and check list were developed on-line (*i. e.*, via *Google Drive*), a methodologic manual was drafted up, and a pilot test was performed with two SRs (one a Cochrane and the other a non-Cochrane). From the results of that test, the issue of the correct nature of the evaluation criteria was returned to the ITT reviewers for consideration, who in a workshop personally standardized those norms. The final form of the evaluation consisted in a qualification of the internal validity and mode of management of the potential sources of sampling bias in a given SR. The internal validity of the SR was evaluated within 5 different domains on a scale of 1 through 6.

The degree to which the potential sources of sampling bias were minimized was qualified on a scale of 0 through 2 (0 = no minimization, 1 = a partial minimization, and 2 = an adequate minimization). Where the qualification was 0 or 1, the extent to which the potential sources of bias affected the results of the SR was assessed. On the basis of these criteria, 43 SRs were finally chosen because of their high quality.

Synopsis of the evidence

Prevention of ROP

The clinical questions (CQs) on the prevention of ROP were answered by evidence from SRs of high quality that addressed the issues concerning each one of the aspects under consideration. In certain instances, the evidence was direct (*i. e.*, stating the enhancement or reduction of the risk of ROP associated with a given factor—for example, oxygen therapy), while in other examples indirect evidence was provided (*i. e.*, citing an enhancement or reduction of rick by a factor that exerts an influence on the frequency of ROP—for example, proper hygiene of the hands leading to a reduction of the nosocomial infections associated with a greater risk of ROP).

For the synopsis and evaluation of the quality of evidence contained in each of the SRs as judged by the methodologic criteria of SIGN (*i. e.*, + or ++), the considerations proposed by GRADE were employed—namely, assessments were made on the basis of the following criteria: [ix]

- (1) Methodologic limitations in the trials included in estimating the effect of the intervention in question on the incidence of ROP that either over- or underestimated that influence—resulting in a lower quality assessed in view of such shortcomings;
- (2) Consistency among the trials—resulting in a lower quality assessed in the face of inconsistency or heterogeneity among the results from the trials included with respect to the evaluation of ROP;
- (3) Direct evidence—when an effect is compared between two parallel interventions (for example, the so-called *head-to-head* comparisons with two different pharmacologically active drugs)—with this form of evidence being considered of higher quality; or indirect evidence—when an intervention is compared to placebo administration—with that type of evidence being regarded as of lower quality;
- (4) Precision of the estimation, with a lower-quality assessment obtaining either when the estimation is imprecise—with the degree of precision being evidenced in the width of the confidence intervals—or when the number of SRs included is very reduced, thus reflecting in a lower statistical significance;
- (5) Presence of a publication bias—with a lower quality assessment resulting in the face of a risk of such bias;

On the basis of these criteria, the experts in methodology of the ITT categorized the quality of the extant body of evidence on the effect of practice on the incidence of ROP according to the categories listed in Table 1.

Table 1. Quality level of the evidence according to the GRADE methodology

QUALITY LEVEL	SYMBOLOGY	SIGNIFICANCE
HIGH	⊕ ⊕ ⊕ ⊕ ○	Low probability that new investigation will modify the confidence level in the estimation of the effect
MODERATE	⊕ ⊕ ⊕ ○ ○	Reasonable probability that new investigation will have a significant impact on the confidence level in the estimation of the effect and modify the latter's magnitude
LOW	⊕ ⊕ ○ ○ ○	High probability that new investigation will have a significant impact on the confidence level in the estimation of the effect and modify the latter's magnitude
VERY LOW	⊕ ○ ○ ○ ○	Any estimation whatsoever is quite uncertain.

Screening for ROP

The CQs regarding the screening for ROP are answered through evidence contained in the British CPG as the source (recommendations A or B) by means of the methodology detailed in the *Guidelines for the Adaptation of Clinical-Practice Guidelines*. In order to facilitate the identification, translation, transcription, and analysis of the recommendations in response to the CQs on the screening for ROP, the corresponding tables of the CPG and SRs. Some of the CQs concerning screening were updated with evidence provided from recent SRs that, for their part, complied with the quality standards required.

Treatment of ROP

The CQs regarding the treatment of ROP are answered through evidence contained in the British CPG as the source (recommendations A or B) by means of the methodology detailed in the *Guidelines for the Adaptation of Clinical Practice Guidelines*. In order to facilitate the identification, translation, transcription, and analysis of the recommendations in response to the CQs on the screening for ROP, the corresponding tables of the CPG and SRs. One of the CQs—it related to the use of Bevacizumab—was answered by means of a "*de-novo* formulation" from evidence provided by high-quality clinical trials.

Follow-up of ROP

The CQs on the follow-up of ROP could not be answered with evidence of high-quality methodology because neither did the British guidelines that were the source contain recommendations A or B nor was an SR identified that provided an answer to the CQs posed by the ETI.

On consideration of the relevance that these CQs had to the longer-term results for the preterm NBs that presented with ROP, the ITT decided to formulate a group of

recommendations based on the opinion of experts, which answers are presented in an independent chapter.

Formulation of the recommendations

Independently of the method employed to evaluate and synthesize the evidence, the recommendations in the chapters on the prevention, screening, and treatment of ROP were formulated on the basis of the 3 criteria proposed by GRADE. (Table 2)

Table 2. The criteria from GRADE employed for the formulation of recommendations

CRITERIA	DESCRIPTION
BALANCE OF RISKS AND BENEFITS	When this balance represents a significant difference between those two opposite outcomes, a strong recommendation is most likely to be formulated; if the balance is more equilibrated, a weak recommendation is the more appropriate.
QUALITY OF THE EVIDENCE	Evidence quality depends on the degree to which the estimation of the effect on the key outcomes can be confided in. When the quality is high, the formulation of a strong recommendation is more probable; and, conversely, if the quality is low a weak recommendation becomes more likely. Nevertheless, situations do exist that justify a strong recommendation solely on the basis of evidence of low or very low quality.
APPLICABILITY TO THE HEALTHCARE SYSTEM AND COSTS*	An elevated cost decreases the likelihood of formulating a strong recommendation in favor of an intervention; conversely, a low cost increases the probability of formulating a strong recommendation. Influences other than the cost are also considered that can affect the applicability of a recommendation in the Argentine healthcare system—such as, for example, the organization and coordination of the services, the availability and qualification of the human and material resources, and the characteristics of the target population.

*Although GRADE proposes a consideration solely of costs, the ITT decided to take into account, in addition to costs, other aspects that could affect the applicability of a recommendation within the Argentine-healthcare system; such as, for example, the general organization and the material and human resources.

From these criteria for evaluation, the ITT defined the strength and valence of the recommendation (Table 3). Table 4 explains the significance of the strength of the recommendation.

Table 3. Strength and direction of the recommendation

		STRENGTH OF THE RECOMMENDATION	
		STRONG	WEAK
DIRECTION OF THE RECOMMENDATION	FOR	↑↑	↑
	AGAINST	↓↓	↓

Table 4. Strength of the recommendation

	Strong recommendation	**Weak recommendation**
Fort the patients	The majority of the persons would be in favor of the recommended intervention with only a small fraction dissenting	The majority of the persons would be in favor of the recommended intervention with a significant fraction dissenting.
For healthcare professionals	The majority of the patients should receive the recommended intervention.	Recognizing that different options are appropriate for different patients, the physician must therefore assist each patient to reach the decision most consistent with that person's values and preferences.
Fort he managers	The recommended intervention can be adopted as a healthcare policy in the majority of the situations.	The necessity arises of conducting a key debate among the groups of interest.

On the basis of the type of that supported each recommendation, those proposals were categorized as follows:

- **Evidence-based recommendations:** recommendations supported by direct evidence of moderate or high quality on the effect of a risk-*vs*.-protection factor or of a particular treatment on the incidence of ROP.
- **Recommendation adapted from the British CPG:** In the instance of a recommendation that the ITT adopts from the CPG of the British Royal College (without modifications), the classification of the evidence is regarded as equivalent to that of the recommendations proposed by SIGN and those considered by GRADE.
  The type-A recommendations are interpreted as strong and the type-B weak, except in certain exceptional examples where the ITT might identify justifiably positive aspects involving dramatic benefits, patient or family preferences, or applicability and thus consider that type-B recommendation as strong.
- **Points of good clinical practice (PGP)** are those recommendations formulated by the ITT on the basis of:
  - Indirect evidence of moderate or high quality on the effect of a risk-*vs*.-protection factor or of a particular treatment on the incidence of ROP
  - Evidence of the effectiveness or safety of the intervention in question on a result other than ROP. With certain interventions, ROP is considered as a secondary result. A considerable number of those interventions would exert no effect whatsoever on the incidence of ROP, while others, such as those resulting in pulmonary disease or mortality, would have profound consequences. Since the search for and analysis of evidence considered only SRs that included ROP in the results—and in view of the possibility of a bias in selection—the ITT decided to formulate those recommendations as **points of good clinical practice**.

- Low-quality or local evidence, the latter being provided by the registry of the ROP Program of the National Ministry of Health

- **Opinion of experts:** recommendations formulated on the basis of the opinion of the members of the ITT

Final Consensus on Adaptation

First Round—virtual

Once the preliminary recommendations were formulated, the same methodology was applied for validation by the remaining members of the ITT. This evaluation enabled the establishment of the degree of consensus on the quality of the evidence and the strength and direction of the recommendation as defined by the GRADE system. Once again. a database and format for data loading were developed and employed on-line (via *Google Drive*)

An analysis of the degree of concordance was performed according to the following rules:

- (1) When the number of discordant evaluations did not exceed that of the concordant, a consensus was considered to have been reached by the ITT. If the quality of the evidence was low, insufficient, or nonexistent but reasons were found to grant the intervention in question a strong recommendation (*i. e.*, inconsistently), that action required a justification of the decision by consensus among the ITT members. The occurrence of such a circumstance was possible in the examples where the sources of the evidence were of high quality, such as the British CPG or a reliable SR, even though the intervention was not among the points of good clinical practice—barring well justified exceptions.

- (2) Dissent among the ITT members was considered to exist when the number of discordant evaluations exceeded that of the concordant. In such situations, the nature of the action taken depended on the magnitude of the discordance.

- (2.1) When the discordance was greater than 70% (an approximation of ⅔= 67%) of the opinions, the degree of disagreement was regarded as HIGH. This circumstance required a meeting to resolve the ITT consensus, which occasion necessarily produced a record of the justification of the final plenary decision. In a similar manner, if the quality of the evidence was low, insufficient, or nonexistent but reasons were found to grant the intervention in question a strong recommendation, that situation required a plenary meeting of the ITT for the same purpose.

- (2.2) When the discordance was less than 70% (an approximation of ⅔ = 67%) of the opinions, the degree of disagreement was regarded as LOW In this instance, the recommendation was maintained as initially proposed, and the ITT proceeded in the same manner for arriving at a consensus as in the previous circumstance since, even in this situation, the course of action required justification.

- (3) During this stage in the evaluation of interventions, the assessors could make commentaries on the barriers and/or facilitative aspects that had been identified, which input could include items of information for consideration during the plenary meetings for purpose of consensus.

- (4) For their part, these inputs—like those arising from the ITT's interaction and the registry of justification during the meetings for consensus—could be included in each recommendation as footnotes in the form of ***notes of application*** in order to overcome barriers in the local adaptation and implementation of the recommendation.

Analysis of the dissent

On the basis of the analysis of dissent concerning a given individual recommendation, the degree of discordance was determined and, as a consequence, that recommendation's position within the distribution of all those evaluated registered along with the measures required to achieve a final consensus.

Second Round—in person

During a plenary formal meeting, the ITT members together debated and reevaluated the discordances to reach a final consensus, in the process acting explicitly according to the specific measures required—*e. g.*, no modification, modification of the strength of the recommendation, citation of a justification for the modifications adapted and composition of notes of application (as detailed above).

From the results of this plenary session, the methodology team made the necessary final adjustments of the recommendations to increase the correlation between the quality of the evidence and the strength of the recommendation.

Third Round—virtual

In a final step, the proposed adjustments were accepted by consensus, according to the consideration of each evaluator either in person or via *e-mail*.

In this manner, with the iterative process to reach a formal consensus having been completed, the final collection of the recommendations within each one of the categories established in the formulation step was obtained. This list was drafted into a preliminary CPG that was presented at the XIII National ROP Workshop in September 2014 in Buenos Aires, where 300 ROP professionals (neonatologists, ophthalmologists, and nurses) convened. These team members, who were considered the users, were given a CD containing that CPG.

Evaluation of the applicability by users

Between October and December of 2014, these professionals, now considered the users, were sent a set of instructions along with a request to respond to a questionnaire (via a format for data loading on-line in *Google Drive*) concerning barriers to or facilitative aspects for the applicability of the CPG.

From these professional users nationwide, 35 responses were received that were duly analyzed and many incorporated into the CPG.

External evaluation

In October 2014, the preliminary CPG and a set of instructions were sent to 5 experts in the field from different professions—3 from Argentina and 2 from abroad—requesting an independent evaluation of the CPG that involved their opinion on the quality of the evidence, the degree of their recommendation, and the barriers to the CPG's applicability as perceived by them—along with a declaration regarding conflicts of interest.

By January of 2015, the responses of those experts were all received and their commentaries included in the guidelines. No conflicts of interest were declared.

Methodologic evaluation

In December 2014 the CPG was presented to the National Program for the Guarantee of Quality in Medical Care (Programa Nacional de Garantía de Calidad de la Atención Médica) of the National Ministry of Health for the purpose of receiving an analysis and obtaining an eventual approval of the program.

The CPG was furthermore evaluated by two methodologies that in addition sent it for consultation and analysis by GRADE and applied the instrument AGREE II to the CPG as well.

The last step was to analyze all the proposals and incorporate the relevant and appropriate corrections in order to arrive at the final GPC in June 2015.

References of General Methodology

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FINAL RECOMMENDATIONS

For this present summarized version of the GPC for translation into English, all the detailed analyses of the evidence on the prevention, diagnosis, treatment, and follow-up of ROP have been excluded, and only the final recommendations are presented in Table 5.

The complete original version of the CPG can be seen at:
http://www.msal.gob.ar/images/stories/bes/graficos/0000000723cnt-guia-pract-clin-ROP-2015.pdf

Table 5. Final recommendations

References: For the recommendations based on evidence (reformulated or adopted), the strength and valence are indicated by the descriptive signs and colors from the GRADE methodology.

✶ Key recommendations; **PGP**, point of good clinical practice; ✓ recommendation based on the opinion of experts

PREVENTION OF ROP	
	RECOMMENDATION
1.1.	PREVENTION OF ADVERSE EFFECTS OF PREMATURITY
1.	**In preterm NBs, what are the RFs vs. the PFs that cause and/or enhance vs. reduce the incidence of ROP?**
✶ PGP	*Adequate measures should be applied for the prevention, diagnosis, and treatment of ROP in all preterm NBs of BW less than 1,500 g and/or of GA less than or equal to 32 weeks.* *Commentary: Included in this group should be those Unusual cases (Ucs) consisting in NBs of BWs 1,500 g or more and/or GAs greater than 32 weeks along with the associated RFs of O_2 therapy, IUGR or extrauterine-growth restriction (EUGR), transfusions, sepsis, and the early administration of erythropoietin (EPO).*
PGP	*A single series of corticoid (dexamethasone or betamethasone) should be administered prenatally to all pregnant women at risk of premature birth during the 24th* through the 34th week of gestation, even though no association of that intervention with a reduction in the incidence of ROP has been demonstrated. (two intramuscular injections of 12 mg of betamethasone administered 24 h apart or 4 such injections of 6 mg of dexamethasone at 12-h intervals)* *Commentary: This procedure is recommended owing to the significant benefits of reductions in*

	mortality and morbidity associated with ROP (i. e., hyaline-membrane disease [HMD], O_2 use, intraventricular hemorrhage [IVH], NEC, and sepsis) along with the lack of adverse effects on the mother or fetus and the facility and economy of the intervention *(*)The current thinking on this point is that women at 23 weeks of gestation should be included as well since fetal viability begins at that week.*
PGP	*A continuation of the series of prenatally administered corticoids beyond the 34th gestational week for pregnancies at risk of premature parturition is advisable when the risk of precocious birth persists at that time (at the same intramuscular dose as in the original series and to be repeated weekly thereafter).* *Commentary: This procedure is recommended owing to the benefits of significant decreases in the interventions to reduce mortality and morbidities (i. e., HMD, O_2 use, IVH, NEC, and sepsis)—that, for their part, are RFs for ROP—along with the lack of adverse effects on the mother or fetus and the facility and economy of the intervention.*
PGP	*An administration of surfactant to those specific preterm NBs who, being symptomatic of respiratory-distress syndrome (RDS) must be intubated, is recommended in spite of their having been previously stabilized through continuous positive airway pressure (CPAP).* *Commentary: Although this intervention is not associated with a decrease in the risk of ROP, the procedure is recommended owing to its correlation with a lower risk of chronic pulmonary disease (CPD) or death.*
PGP	*The use of ibuprofen or indomethacin prophylactically in premature NBs for closure in patent ductus arteriosus (PDA) is not recommended* *Commentary: That intervention not only does not decrease the risk of ROP but also is associated with adverse gastrointestinal and renal effects. Moreover, a high percentage of the PDAs become closed spontaneously at postnatal Day 3.*
PGP	*The use of ibuprofen or indomethacin intravenously in the treatment of PDA that is hemodynamically significant is advisable (dosage protocols: for **indomethacin**, 3 of 0.2-mg/kg doses every 12 h; for **ibuprofen**, an initial 10-mg/k dose followed by doses of 5 mg/kg at 24 and 48 h).* *Commentary: Although not associated with a reduction in the risk of ROP, this intervention is justified in order to close a PDA.*
PGP	*The use of prolonged courses of treatment with indomethacin is not recommended in order to close a PDA in premature NBs.* *Commentary: Extended courses of treatment with indomethacin neither reduce the incidence of ROP nor exhibit differences in the closure, reopening, or need for surgical ligation of a PDA, while at the same time increasing the risk of NEC.*
↓↓	*The routine intravenous supplementation with vitamin E is not recommended*

	in premature NBs. *Commentary: Although vitamin E reduces the risk of intracraneal hemorrhage, severe ROP, and blindness (but only in NBs of BW below 1,500 g); the intervention significantly increases the risk of sepsis.*
1.2.	**INFECTION PREVENTION**
PGP	*Maintaining the hand washing at all times is absolutely imperative.* *Commentary: Even though insufficient evidence has been obtained to demonstrate the effectiveness of hand-washing, the practice still constitutes one of the principal strategies to reduce hospital-acquired infections (HAIs) and the consequent incidence of ROP and morbimortality.*
PGP	*An implementation of the available methods for the rational use of antibiotics during the neonatal period is recommended* *Commentary: Although no evidence is currently available for evaluating the rational use of antibiotics specifically with premature NBs in reducing HAIs and secondarily the incidence of ROP, the rational use of antibiotics has definitely been shown to decrease the incidence of HAIs in general and would thus be warranted in such NBs as a prophylactic measure.*
PGP	*Safe means of using central venous catheters must be implemented* *Commentary: No evidence is available on the implementation of specific methods of using catheters in order to avoid HAIs in premature NBs and thus, secondarily, reduce the incidence of ROP. Nevertheless, central venous catheters are major sources of infections in these NBs.*
↑	*When exogenous lactoferrin is not available, the enteric feeding of colostrum and human milk (HM) to preterm NBs is recommended.* *Commentary: This alternative is advisable because of the anti-infective properties of the lactoferrin in human milk and the consequent reduction in the risk of ROP.*
1.3.	**PREVENTION OF EXTRAUTERINE-GROWTH RESTRICTION**
✶ PGP	*Especially with premature NBs that present poor postnatal gains in weight (i. e., EUGR), the utmost measures of prevention, diagnosis, and treatment of ROP should be undertaken.* *Commentary: These precautions are recommended owing to the greater risk of ROP incurred by NBs exhibiting subnormal growth kinetics.*
PGP	*Since GA and BW—independently of any restriction in extrauterine growth—are indicators for the screening for ROP in a preterm NB, weight gain during the first weeks should not to be considered the sole criterion.*
PGP	*Early trophic feeding of premature NBs is suggested—if possible during the first day of life—with HM, either fresh or from the bank; or alternatively, with milk constituted from a formula if the former are not.* *Commentary: The recommended dose is from 15 to 25 ml/kg/day in NBs of BW less than 1,000 g and from 20 to 30 ml/kg/day in NBs of BW greater than 1,000 g administered by gavage tube, for a*

	suggested duration of 3 to 5 days. Thereafter the doses are increased by 20 to 30 ml/kg/day for both weight classes of NBs until the time of total enteric feeding (at 160 to 200 ml/kg/day).
PGP	*The implementation of all possible strategies is recommended for feeding the preterm NB with its own mother's milk.* *Commentary: The strategies for doing so include: a breast-pumping room for the extraction of maternal milk, the provision of breast pumps therein, facilitation for the mothers of the necessary period of residency in the hospital, non restricted access of the mothers to the NICU, and promotion of skin-to-skin contact. Should the maternal milk not be available, the use of HM from the bank is recommended.*
PGP	*The supplementation of HM with fortifiers or with probiotics might be considered (though those latter products happen to be unavailable in our country).* *Commentary: Although no evidence has been found that the supplementation of milk fed to premature NBs with fortifiers or probiotics decreases the risk of ROP, the former could diminish EUGR and the latter reduce mortality and the risk of NEC.*
PGP	*In preterm NBs in the NICU, the initiation of complete parenteral nutrition is indicated from the time of birth in combination with the enteral nutrition.* *Commentary: Even though no evidence is available that this form of dual nutrition reduces the risk of ROP, that recourse constitutes a strategy to prevent deficits in amino acids (AAs, with those required at levels of 4 g/kg/day) and energy (required at 90–110 kcal/kg/day) with an aim at decreasing EUGR.*
1.4.	**PREVENTION OF ANEMIA**
PGP	*A delayed umbilical-cord clamping should be recommended in preterm NBs.* *Commentary: Although no evidence exists that this measure reduces the risk of ROP, nevertheless that delay is associated with a lower need for transfusions because of anemia, a greater circulatory stability, and a lower risk of IVH of all grades and NEC.*
PGP	*Low hemoglobin and hematocrit levels should be used to indicate transfusions.* *Commentary: Although no evidence has been garnered that a restriction in the use of transfusions reduces either the risk of ROP or morbidity and mortality, nevertheless that limitation and could, at least secondarily, reduce the risk of ROP.*
PGP	*The number and volume of blood extractions for laboratory studies should be kept to a minimum in favor of using micro techniques and noninvasive methods of monitoring.* *Commentary: Although the minimization of blood extractions has not been shown to reduce the risk of ROP, that precaution does, in fact, decrease the risk of anemia and the subsequent need for transfusions*
↓↓	*The early administration of erythropoietin-EPO (before the eighth day of life) must be avoided because that intervention significantly increases the incidence of severe ROP.*

	Commentary: Although erythropoietin administration reduces the number and volume of subsequent transfusions, the clinical impact is minimal.
↑	*The use of erythropoietin-EPO at a later time (on or after the eighth day of life) can be considered since from that point on no correlation with an increase in ROP has been demonstrated.* *Commentary: Although erythropoietin administration has been associated with a modest reduction in the need for subsequent transfusions, the intervention has not been correlated with a decrease in morbimortality in preterm NBs nor with a risk in exposure to bank blood, since many of these preterm NBs have already received a transfusion during the first week of life.*
↑	*An enteral iron supplementation should be considered for preterm NBs at a dosage of 2 to 3 mg/kg/day from the second postnatal week on.* *Commentary: Although iron supplementation does not reduce the frequency of ROP in premature NBs, that intervention decreases the risk of iron-deficiency anemia.*
1.5.	**OXYGEN-THERAPY MANAGEMENT**
PGP	*With preterm NBs in the delivery room, for beginning the resuscitation, positive-pressure ventilation (PPV) with low O_2 levels (between 30% and 50%) is recommended along with a constant monitoring of percent saturation of O_2 at all times.* *Commentary: Although no differences have been reported in the incidence of ROP at different concentrations of O_2 employed in the resuscitation of NBs, this recourse increases their survival.*
PGP	*Delivery rooms should be provided with air-O_2 blenders and pulse oximeters for the regular monitoring of O_2-saturation levels and for reaching the following indicated values at:* *3 min: 70%–75%* *5 min: 80%–85%* *10 min: 85%–95%*
PGP	*O_2 levels can be adjusted (i. e., increased or decreased) every 90 sec, with the parameters expected at 3, 5, and 10 min taken as reference values.*
✶ ↑↑	*With all of the preterm NBs administered O_2, a **continuous** monitoring of O2-saturation levels, with no interruption whatsoever, must be performed at all times with a pulse oximeter to maintain the level at between 89% and 94% with an alarm set for a minimum level of 88% and a maximum of 95%.* *Commentary: These norms should be observed with any and all systems of O_2 provision (via mechanical ventilator in any mode, CPAP, O_2 hood, nasal cannula, or free breathing, in any and all circumstances (i. e., neonatal hospitalization, patient transportation, surgery, or anesthesia), and*

	independently of the duration of O_2 therapy.
PGP	*All the NICUs should be equipped with air-O_2 blenders and environmental oximeters so as to be able to control periodically the fraction of inspired O_2 (FiO_2,), especially when a discrepancy occurs between the mixture that is indicated and the percent saturation obtained.*
PGP	*For endotraqueal suctioning should be used a resuscitation bag connected to an air-O_2 blender.* *Commentary: This arrangement is prescribed so that during the intervention the NB receives the same air-O_2 mixture that was used previously; and in order to avoid episodes of hypoxia or hyperoxia, other strategies should be considered (e. g., increasing the maximal inspiratory pressure in the airway [MIP] and the breathing rate [BR]) instead of "preoxygenating" the NB by elevating the FiO_2.*
PGP	*Two types of flowmeters are also needed: the standard type for 15 l/min and one calibrated for the slow flow rates of 1 to 3 l/min.* *Commentary: The low-flow-rate meters should be used with nasal cannulas. With an O_2 hood, the flow should be 8 to 10 l/min and a minimum of 5 l/min for the smallest patients. With CPAP, the use of the lowest flow is advisable in order to attain the necessary positive end-expiratory pressure (PEEP).*
1.6.	**ALLEVIATION OF PAIN**
PGP	*The use of nonpharmacological methods to reduce pain (e. g., administration of sucrose or maternal milk, either artificially or through breast feeding, the kangaroo-care method) is recommended when routine procedures that are painful must be employed with NBs.* *Commentary: Although no evidence exists that such pain-reduction measures reduce the incidence of ROP, non pharmacologic analgesic techniques have been demonstrated to improve the well-being and stability of NBs.*
1.7	**STRESS PREVENTION**
PGP	*For stress reduction, the implementation of methods for "developmental care" such as nesting and sensory stimulation, are recommended.* *Commentary: Though such methods do not diminish the incidence of ROP, those techniques contribute to the well-being of the preterm NB and could improve its neurologic development.*
PGP	*A lowering of the room lighting during the rest periods of preterm NBs are advisable though that practice does not reduce the incidence of ROP.*
2.	**What is the effectiveness and reliability of the screening for ROP in reducing the severity of the sequeelae and in improving the quality of life of the preterm NB?**

2.1.	**STRATEGIES IN THE SELECTION OF PATIENTS BY BW, GA, AND PATHOLOGY**
✶ ↑↑	*Screening for the detection of ROP is recommended in each and every NB of BW <1,500 g and/or GA 32 weeks or less as well as those of between 33 and 36 weeks of GA at whatever BW who present with at least one of the characteristics identified as RFs for ROP.* *Commentary: The most significant RFs are O_2 therapy, either IUGR or EUGR, transfusions, sepsis, and early administration of EPO.*
✶ PGP	*The utmost measures are recommended for the prevention, diagnosis, and treatment of ROP in premature NBs having manifested IUGR and who are born weighing more than 1,500 g or at GAs of more than 32 weeks.* *Commentary: These criteria are cited because NBs presenting with such RFs are the most likely to develop pathology leading to ROP.*
2.2.	**TIME COURSE FOR ROP SCREENING**
✶ ↑↑	*The following scheme is recommended for the first examination in ROP screening:*

GA at birth (in weeks)	*Start of ophthalmological examinations (in postnatal weeks)*
22	9[a]
23	8[a]
24	7[a]
25	6[a]
26	5[a]
27	4[a]
28	4[a]
29	4[a]
30	4[a]
31	3[a]
32	2[a]
33	2[a]

✶ ↑↑	*NBs of GAs greater than 33 weeks who have received O_2 therapy or presented RFs should be examined within 1 to 2 postnatal weeks in order to confirm that the retinal vascularization has been completed.* *Commentary: Once retinal vascularization is complete, the continuation of ophthalmic examinations is unnecessary. Otherwise, the examinations are to be continued according to the indications of the ophthalmologist.* *If a NB under observation receives hospital release on the basis of other considerations before the ophthalmology control, the observation must be conducted before leaving the hospital.*
✶	*A repeat of the screening every week is recommended, but more frequently if*

↑↑	*the following characteristics are observed:* *- Stage-3 ROP in any zone of the retina* *- Any stage of ROP in zone I or posterior zone II* *- The presence of ROP plus* *- The presence of aggressive posterior ROP* *- Immature vascularization in zone I or posterior zone II* *<u>A screening every week or every two weeks:</u>* *- Immature vascularization in posterior zone II* *- Stage-II ROP in zone II* *- Improving ROP in zone I* *<u>A screening every two weeks</u>:* *- Stage-1 ROP in zone II* *- Immature vascularization in zone II* *- Improving ROP in zone II* *<u>A screening every three weeks</u>* *- Stage-1 or -2 ROP in zone III* *- Improving ROP in zone III*
PGP	*An adequate registration of the results of each ophthalmic examination should be made detailing the zone, stage, and extension (in indications of o'clock within the zone) of any type of ROP along with the presence of preplus or plus disease.* *Commentary: These records should include the recommendation concerning the time when the next examination is to be performed (if necessary) and should be noted down in the NB's clinical history.* *Before performing the first ophthalmic examination, the NB's parents should be informed, both orally and in writing, about the details of the screening procedure.*
↑↑	*The ophthalmic examinations should be discontinued in ROP-free NBs once the vascularization has extended into zone III.* *Commentary: The examinations are discontinued at this stage of retinal development because from that point on the risk of developing a form of ROP that could impair vision is minimal. This situation usually occurs after 36 weeks of postmenstrual age.*
PGP	*In the presence of ROP, the screening of the active disease should be discontinued when any of the following characteristics are observed in at least 2 successive examinations:* *- No further increase in disease severity;* *- Partial disease resolution becoming complete;* *- Change in color of the ridge from salmon pink to white;*

	- Transgression of vessels through the demarcation line; *- Commencement of the process of replacement of active ROP lesions by scar tissue.* *Commentary: Once the screening of ROP that is potentially treatable is finalized, the ophthalmic examinations can be continued if the ophthalmologist considers that a probability still exists in identifying significant ophthalmic sequelae that are potentially treatable.*
2.3.	**PREPARATION OF THE NEWBORN FOR THE SCREENING**
PGP	*In order to prepare the NB for the ROP screening, the pupil should be dilated by instilling a drop of an aqueous solution of 5% phenylephrine, 0.5% tropicamide in each eye, in 2 or 3 doses separated by an interval of 15 min.*
PGP	*The lowest amount possible of the mydriatic drops should be used for pupil dilation, while at the same time monitoring the NBs blood pressure and heart and breathing rates.* *Commentary: These precautions are suggested in order to minimize the possibility of absorption of the drugs by other tissues outside the eye and control of a possible greater systemic effect.*
↑↑	*The instillation of anesthetic drops before the ophthalmic examination is also recommended (of 0.5% aqueous proparacain, 1 to 2 drops 30 to 60 sec beforehand), especially if a palpebral separator (a speculum) is to be used.*
↑↑	*The use of other techniques to increase the comfort of the NB during the ophthalmic examination for ROP screening are also recommended; such as the administration of a solution of sucrose, rocking the infant, wrapping it up in a sheet, and/or the use of a pacifier.*
PGP	*The ophthalmic examination for ROP screening should also be as short as possible and the necessary precautions taken to resolve promptly and efficiently any situation involving a risk that might occur, such as adverse effects on the blood pressure and/or the heart and breathing rate of the NB.*
2.4.	**ROP SCREENING BY BINOCULAR INDIRECT OPHTHALMOSCOPE (BIO) AND RETCAM (REMOTE DIGITAL IMAGING)**
✶ ↑↑	*The use of a binocular indirect ophthalmoscope (BIO) for ROP screening is recommended.* *Commentary: Alternatively, systems for obtaining digital images could be used when ophthalmologists trained in the diagnosis of this pathology are not available, since such an approach would enable the transfer of those images to remote diagnostic centers where such specialists are present. In addition, that technique can prove useful both in documenting objectively the findings in*

	the back of the eye and in providing a permanent record for the purpose of teaching and research.
↑↑	*The use of a palpebral speculum along with a scleral depressor is recommended in order to visualize the peripheral regions of the retina.* *Commentary: The blood pressure, heart rate, and percent O_2 saturation should be monitored at the same time because those parameters could decrease during this intervention.*
↓↓	*The use of 70% aqueous isopropanol or 4% aqueous chlorhexadine gluconate as disinfectants for the scleral depressor or the palpebral speculum should be avoided.* *Commentary: These disinfectants should not be used because they are not effective with adenovirus, which pathogen can cause a lethal infection in NBs*
PGP	*The scleral depressor and palpebral speculum should rather be disinfected by washing the instruments in water with detergent followed by immersion in 70% aqueous ethanol for 5 to 10 min.* *Commentary: After the disinfecting, the instruments can be conveniently dried with a sterilely packaged gauze before further use.*
3.	**In preterm NBs with severe ROP, what is the effectiveness and safety of the treatment criteria indicated according to the diagnosis of severity with respect to the cure, remission, or reduction in the onset of complications and sequelae in this disease?**
3.1.	**CRITERIA INDICATING THE FORM OF TREATMENT IN SEVERE ROP**
✶ ↑↑	*Treatment of ROP must be performed upon the presentation of any of the following pathologies:* *- Zone I: any stage ROP with plus disease* *- Zone I: stage-3 ROP without plus disease* *- Zone II: stage-3 ROP with plus disease*
✶ ↑	*Upon presentation of stage-2 ROP plus in zone II, the treatment of ROP should be undertaken.*
✶ PGP	*The NBs having aggressive posterior ROP should be treated within 48 h of the diagnosis. In the rest of the cases, the treatment should be undertaken within 72 h.* *Commentary: This difference in ophthalmologic urgency is recommended because aggressive posterior ROP exhibits a more rapid and serious development than the other manifestations of the disease. In those latter cases requiring treatment, the most favorable outcomes are likewise still always assured by the greatest possible avoidance of delays.*

PGP	*The attending ophthalmologist should explain to the parents the necessity of the treatment and obtain their written informed consent before carrying out the procedure.*
PGP	*Some 95% of preterm NBs are released from the hospital without their complete ophthalmologic follow-up control.* *Those patients must be readmitted to a neonatal service with an NICU (or else a pediatric service) for further treatment.*
3.2.	**DIODE-LASER TREATMENT VS. OTHER INTERVENTIONS**
✶ ↑↑	*Transpupillar diode-laser treatment is recommended as the first line of treatment for ROP.*
PGP	*Diode-laser treatment is best performed in the same neonatal unit, and with the NBs under sedation and analgesia.* *Commentary: The treatment can also be done in an operating room under general anaesthesia, but this scenario would involve a delay and require a pediatric anaesthesiologist along with the control of a neonatologist and a trained nurse.*
PGP	*A topical anaesthetic should not be the only means of providing anaethesia during the diode-laser treatment of ROP.* *Commentary: During the diode-laser treatment of ROP, the NB should be in a state of either sedation with analgesia or anaesthesia.*
PGP	*The diode-laser treatment should be performed within 48 to 72 h of the diagnosis of ROP (according to the severity of the disease).* *Commentary: If the NB is in an NICU lacking a trained ophthalmologist and the diode-laser equipment for performing the intervention, the treatment can still either be carried out in the same NICU, but with another ophthalmologist and portable equipment, or else be programmed in another center to which the NB would be transported.*
3.3.	**PROCEDURES FOR TREATMENT WITH ANTIANGIOGENICS (BEVACIZUMAB)**
✶ ↑	*The intravitreous monotherapy with bevacizumab (without the necessity of laser photocoagulation) should be considered before the retinal detachment (RD) occurs in stage-3 ROP plus in zone I (but not in zone II) with hemorrhaging, pupilar rigidity, and intravitreous neovascularization (with minimal fibrosis) or in aggressive posterior ROP (AP-ROP)—at a dosage of 0.625 mg applied through the pars plana at 2mm from the limbus.* *Commentary: The application of bevacizumab is performed without laser photocoagulation, since*

	the latter has been shown to have a low percentage of success.
✶ ↑	*Infants treated with bevacizumab should be followed for a prolonged length of time because of the continuing risk of a late recurrence of the disease.*
4.	**In preterm NBs treated for severe ROP, what is the effectiveness and safety of remote follow-up and rehabilitation with respect to a reduction in the incidence of complications and sequelae (*e. g.*, retardation in neurodevelopment, learning disorders, disability in social insertion, reduction in the quality of life)?**
4.1.	**Duration of the long-term follow-up**
✓	*Ophthalmological controls of preterm NBs are recommended at 3, 6, 9, and 12 months corrected age, and subsequently at once or twice per year according to the findings. Infants treated for ROP, these controls should be continued up to adulthood.*
4.2.	**Referral for early visual stimulation (selection of patients and timing)**
✓	*In NBs who have manifested some stage of ROP, a referral for early visual stimulation is recommended beginning during the first months of life and even including right after release from the neonatal service.*
4.3.	**Referral for special education of visually impaired or blind NBs (selection of patients and timing)**
✓	*NBs with visual impairment or blindness should be enrolled as early as possible in a formal educational facility—be it ordinary or specialized—in accordance with the characteristics of their handicap, their family resources, and the educational wherewithal of their community.*

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