What's new for ROP? An outline review of the revised guideline for the screening and treatment of retinopathy of prematurity

This year sees the introduction of an updated Guideline on retinopathy of prematurity (ROP) written by a multidisciplinary Guideline Development Group. The Guideline outlines recommendations for screening newborn babies who are at risk of developing ROP in the UK, and their subsequent treatment. In this article the focus is on the importance of screening for ROP, the need for multiprofessional service provision, and evidence-based treatment.

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Key points

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1. ROP is a potentially preventable cause of blindness in children.
2. The incidence of severe ROP has decreased, despite a growing population of low gestational age babies, indicating the usefulness of the previous ROP screening Guideline.
3. All units must have an ROP screening protocol for all infants born at <32 weeks gestational age (GA) and/or <1501g birthweight (BW).
4. The success of a multi-disciplinary screening programme requires a locally developed integrated care pathway.

Retinopathy of prematurity (ROP) has emerged as a potentially treatable cause of childhood blindness over the last 50 years in the wake of advances in neonatal care. The burden of childhood blindness has massive implications for the future care, education and employment of these children throughout their lifetime.

In the early 1980s, there were less than ten ophthalmologists screening neonates for ROP in the UK (personal recollection). Following the publication proving the efficacy of ROP treatment in 1988[1] the College of Ophthalmologists in association with the British Association of Perinatal Medicine (BAPM) published guidelines for screening and by the mid 1990s the number of ophthamologists performing ROP screening had increased to 183[2]. These guidelines were revised in 1995 to offer guidance on treatment[3].

Has this greatly increased ophthalmic activity reduced the incidence of blindness due to ROP? Between 1969 and 1985 the incidence of ROP-induced childhood vision impairment as a proportion of childhood blindness was stable at 5%, but rose to 8% between 1985 and 1990[4]. The incidence then fell to 3% in 2000[5]. While this reduction has been referred to as a lull in the ROP rates[5], it could be argued that this is due at least in part to increased awareness and the result of successful implementation of screening and treatment programmes. The increased incidence through the 1980s and beyond was due to the increased survival of preterm infants at a time when there was no effective treatment for ROP. Despite further increases in the survival of these premature infants, the incidence of ROP-induced blindness has decreased which could be seen as a partial victory in this hard fought battle against one of the few preventable causes of childhood blindness.

The first Guideline in 1990 was a consensus opinion of the working party based on a single meeting reviewing the limited literature and the working party's own clinical experience. Over time the guidelines have become increasingly evidence-based and have extended to include treatment as well as updated and improved screening strategies.

An audit of compliance to the 1990 and 1995 Guidelines found that 7% of the ophthalmologists screening in the UK used criteria resulting in less babies being screened than was recommended[6]. There are still reports of unscreened or untreated babies[7] and the updated evidence-based document aims to reduce these preventable causes of blindness.

The second revision in 2008 led by the Royal College of Paediatrics and Child Health (RCPCH) in collaboration with the Royal College of Ophthalmologists (RCOphth) and the British Association of Perinatal Medicine (BAPM) is discussed herein. This latest Guideline has been written in response to three major issues. First, a significant revision in the recommendations for treatment reported in 2003[8]; second a revision of the international classification of ROP in 2005[9], and third, it was hoped that new screening criteria could be developed which would reduce the number of babies to be screened.

The Guideline was compiled by a

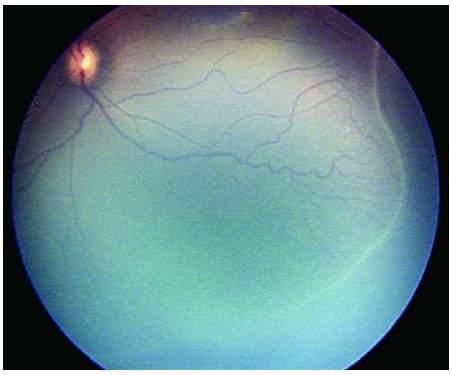

FIGURE 1 Stages 1 and 2 ROP – The demarcation line of stage 1 ROP at the bottom of the image develops into a three dimensional ridge protruding out from the plane of the retina in the upper part of the image – stage 2 ROP.

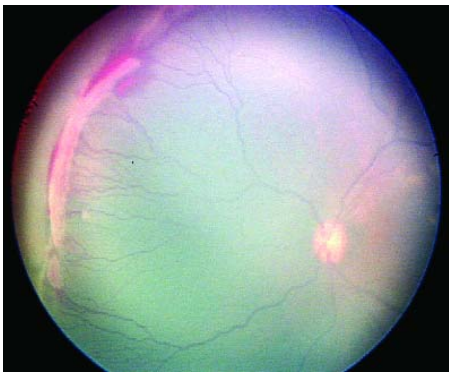

FIGURE 2 Stage 3 ROP – Ridge with extraretinal fibrovascular proliferation, associated here with a small haemorrhage.

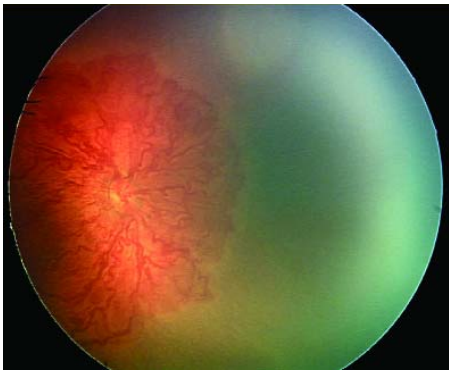

FIGURE 3 Aggressive posterior ROP (Image courtesy of Anna Ells, Alberta Children's Hospital, Calgary, Canada).

multidisciplinary group of ophthalmologists, neonatologists, paediatricians, a paediatric anaesthetist, neonatal nurses, parents of premature babies and representatives from the premature baby charity BLISS. The Guideline followed methodology based on developing clinical questions and systematically searching for and reviewing the published literature to answer these questions. All papers were reviewed by clinical experts. Recommendations were formulated based on the evidence and graded using the SIGN hierarchy[10]. The draft document underwent independent stakeholder consultation.

Stage 1	Demarcation line
Stage 2	Formation of three dimensional ridge
Stage 3	Fibrovascular proliferation at ridge
Stage 4	Partial retinal detachment a) macula on b) macula off
Stage 5	Total retinal detachment
Aggressive posterior ROP – an additional stage introduced by ICROP revisited[9]	

TABLE 1 The stages of ROP.

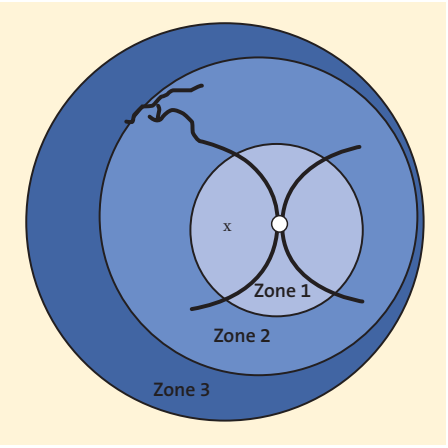

FIGURE 4 Arial image depicting zones of ROP. The central small circle is the optic disc, x marks the macula. Zone 1 extends from the disc to twice the disc-macula distance. Zone 2 extends from the periphery of zone 1 to the nasal ora serrata (peripheral extent of the retina), and to the equidistant area from the disc on the temporal retina. The remaining temporal retina is zone 3. This image shows a patch of ROP developing at the zone 2-3 border superotemporally (upper left of figure).

Background to ROP

ROP is caused by defective retinovascular development in babies who are born early. Premature birth occurs at a time when eye growth is very active and some of these processes, that would normally be occurring *in utero*, can be perturbed in babies born prematurely. Such is the situation with ROP, a condition which only affects the retinal blood vessels as they develop.

ROP develops at the growing edge of the retinal vessels and is seen as a white line (stage 1) which may spontaneously resolve or develop into a three dimensional ridge (stage 2) (**FIGURE 1**). As ROP progresses there is fibrovascular proliferation (stage 3) (**FIGURE 2**) and as it becomes sight-threatening the retinal blood vessels become highly engorged and tortuous, described as preplus and plus disease[9]. A more accelerated form of the disease was recently described as Aggressive Posterior ROP (APROP). This carries a very high risk of blindness if untreated and, as it can be difficult to diagnose, it poses a major challenge (**FIGURE 3**). Eventually the retina may detach, known as stages 4 and 5 characterised by increasing extent of the detachment (**TABLE 1**).

ROP is described by its four features: severity by stage (1-5 and APROP), extent by clock hour, location by zone (I to III) (**FIGURE 4**) and activity by the presence of preplus and plus disease. Knowing in which zone ROP is located is critical because ROP in zone I carries a very high risk of becoming sight-threatening[11], whereas for ROP in zone III this risk is almost nil[12]. Similarly, the presence of plus disease indicates that ROP is highly active and if untreated carries a significant risk of a poor visual outcome[2].

Screening – evidence-based recommendations

Which babies need to be screened?

The former Guideline recommended screening all infants with a gestational age (GA) of less than 32 weeks and/or a birthweight (BW) of less than 1501g. A literature review identified 23 cohort studies used to develop the current screening indications. These studies showed that a reduction in screening criteria from 32 to 30 weeks GA or from 1500g to 1250g BW would have missed two babies requiring treatment. These were however from a Danish cohort from 1982-1987 and it could be argued that neonatal practice has changed so as to eliminate ROP in larger more mature babies. However ophthalmologists on the Guideline group provided data from personal practice confirming that sight-threatening ROP had occurred in eight babies with a BW of more than 1250g and a GA of more than 30 weeks since 2000. As a result the Guideline recommends that all babies less than 31 weeks and/or BW of less than 1251g *must* be screened for ROP, and all babies of GA of less than 32 weeks and/or BW of 1501g or less *should* be screened. The word *should* acknowledges

the relatively weaker evidence for screening babies between 1251g and 1501g BW, and 31 and 32 weeks GA.

The UK Guideline differs from those recently published in the USA[13,14]. It is also important to note that the UK Guideline is applicable to the UK alone and specifically not to those middle human development countries where it has been shown that larger and more mature babies are at risk of developing sight-threatening ROP[15].

Screening examination protocol

The onset and progression of ROP are both largely determined by postmenstrual rather than postnatal age[2,16]. This relatively stereotyped natural history is very helpful when designing a screening programme.

Previously the start of screening was recommended at 6-7 weeks, which was too early for some and possibly too late for others. This has now changed to be tailored to the GA and BW of the baby and is detailed in **TABLE 2**. This recommendation takes into account two issues – the later postnatal age at onset in the smallest babies (i.e. similar post menstrual age (PMA)) and the need to see larger babies before discharge, as the failure to attend rate after leaving the neonatal unit is very high[17-19].

Screening should be at least fortnightly and more frequently if there are signs of impending severe ROP.

Screening criteria for final examination and discharge

One of the critical decisions for a screening programme is knowing when it is safe to stop, thus minimising unnecessary examinations. Examinations can cease once full vascularisation is achieved, or if vascularisation has reached zone III in an eye with no previous ROP and the baby has reached at least 37 weeks PMA. As mentioned, once vessels have reached zone III the risk of sight-threatening ROP has passed. However, it is known that being absolutely certain that the retinal vessels are in zone III can be difficult. For this reason the safety net of 37 weeks PMA has been added because ROP emerging after this time is not known to become severe, and this age criterion is more robust than zone III alone. When progressive active ROP has preceded but not developed into ROP needing treatment, screening can stop when regression characteristics have been seen on two consecutive examinations (**TABLE 3**).

	Timing of first ROP screen	
Gestational age (weeks)	**Postnatal weeks**	**Postmenstrual weeks**
22	8	30
23	7	30
24	6	30
25	5	30
26	4	30
27	4	31
28	4	32
29	4	33
30	4	34
31	4	35

TABLE 2 Timing of first ROP screen by gestational age.

1. Lack of increase in severity of ROP
2. Partial resolution progressing towards complete resolution
3. Change in colour of ridge from salmon pink to white
4. Transgression of vessels through the demarcation line
5. Commencement of the process of replacement of active ROP lesions by scar tissue

TABLE 3 ROP regression characteristics.

At least five continuous or eight cumulative clock hours of Stage 3 ROP in zones I or II, in the presence of 'plus' disease.

This was the indication for treatment 1988 to 2003.

TABLE 4 Definition of threshold ROP.

Care of the baby during screening

For the first time, the 2008 Guideline considered the care of the baby during the screening examination, since this can be uncomfortable, particularly as it frequently involves the use of a speculum and scleral indentor. Newborn Individualized Developments Care and Assessment Programme (NIDCAP)-supported babies are reported to have a faster recovery as measured by salivary cortisol levels than those supported with standard care[20,21]. Topical anaesthesia with oxybuprocaine hydrochloride (trade name Benoxinate or Novesin®) has been shown in one study to reduce the pain as scored by the Premature Infant Pain Profile (PIPP)[22] and is advised for use for all babies requiring speculum insertion. There is conflicting evidence regarding the usefulness of other care techniques for comforting babies during ROP screening such as sucrose administration prior to examination, nesting, swaddling and the use of a pacifier[23]. Despite the uncertainty of the specific nature of these methods of comforting they all promote care by focusing on the baby's wellbeing during and after the examination.

Treatment

Parents or carers should be given the opportunity to speak to the ophthalmic surgeon prior to treatment and should also be provided with written information about the surgical procedure, anaesthesia and the associated risks.

Treatment methods

Cryotherapy of the peripheral retina was proven to be effective in the large multi-centre CRYO-ROP Study[1]. The indication for treatment at that time was 'Threshold ROP' (**TABLE 4**). Since the 1980s there has been an almost total switch over to laser therapy as the preferred treatment modality (**FIGURE 5**). Evidence suggests that diode laser is associated with a better long term refractive outcome than cryotherapy[24], less postoperative ocular and systemic complications, and has the practical benefit of being more easily portable.

After ten years of follow-up the eyes treated with cryotherapy had better structural and visual outcomes compared to controls, but despite this 42.5% of children still had an unfavourable visual outcome[25]. As this outcome was less than ideal, treating babies earlier was investigated and proven beneficial in the Early Treatment of ROP (ETROP) trial[8]. The ETROP study treated prethreshold ROP as defined in **TABLE 5**. The results of ETROP showed an improved outcome both in terms of visual acuity and structural outcomes and resulted in revised indications for treatment (**TABLE 6**)[8]. These revisions have lead to a decrease in the mean PMA of treatment from 37.0 weeks for babies conventionally treated at threshold disease, to 35.2 weeks in those treated at the pre-threshold stage[8].

Aggressive posterior ROP should be treated as soon as possible, and within 48 hours. All other eyes requiring treatment should be treated within 48-72 hours of diagnosis. A clinical decision regarding the fellow eye must be undertaken, balancing the risks of exposing the infant to two

treatments in quick succession. Due to the need for urgent treatment, clinicians might consider ROP screening early in the week to avoid difficulties of mustering a team over the weekend.

The new Guideline acknowledges the complete switch to laser treatment and the revised indication for treatment from threshold disease to plus disease, with the focus directed largely away from peripheral ROP towards central retinal plus disease.

Preparation for treatment

Sedation and analgesia with elective ventilation in the neonatal unit seems the most popular choice of preparation for ROP treatment. General anaesthesia in theatre if time constraints permit is also recommended by the Guideline. However, due to a review of 12 babies undergoing cryotherapy with topical anaesthesia alone, three of whom required resuscitation post treatment, and 75% of whom were unstable during or after treatment, it is recommended that topical anaesthesia alone is not sufficient for ROP treatment[26].

Mydriasis for laser surgery should follow the same drop regimen as for pre screening pupillary dilatation. An environment safe for laser usage is necessary, as is an adequately heated environment and the room must be darkened during treatment. Monitoring during treatment should follow local protocols for safe surgical procedures in neonates. After discharge if a baby requires treatment for ROP, readmission to a paediatric unit with intensive care facilities is necessary.

After treatment

As it takes time for the laser reaction to appear in the retina, the first postoperative examination should be at around seven days. Around 10% of infants require retreatment[8] and this is usually performed within two weeks of the initial treatment. The characteristic features of regressing ROP are listed in **TABLE 3**.

Organisation of services

Communication and responsibilities

The key to delivering an appropriate programme for ROP screening and treatment is good coordination and communication between neonatal and ophthalmic teams and parents. It is the neonatologist's responsibility to refer at risk babies to the screening ophthalmologist and also to be responsible

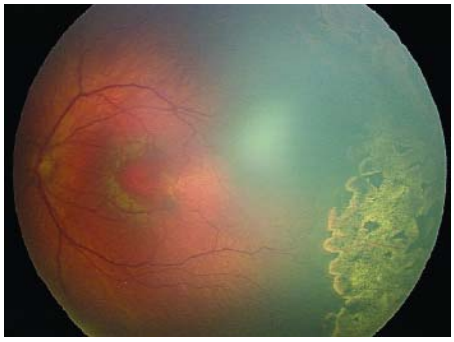

FIGURE 5 Photocoagulation burns to the peripheral retina in an infant treated for ROP.

Zone I, any stage ROP less than threshold
Zone II, Stage 2 with plus disease
Zone II, Stage 3 without plus disease
Zone II, Stage 3 with plus disease, but less than the criteria for threshold disease

TABLE 5 Definition of prethreshold ROP (as used in ETROP trial[8]).

Zone I, any stage ROP with plus disease
Zone I, Stage 3 with or without plus disease
Zone II, Stage 2 or 3 with plus disease
These became the indications for treatment in 2003, replacing 'Threshold ROP' as defined in TABLE 4

TABLE 6 Revised recommendations for treatment.

for continuing care if there is transfer to another unit. How this is organised in detail will depend on local circumstances and resources, and should be clarified by a local written protocol. The Guideline advises that an integrated care pathway should be created in each screening centre and that responsibility should be at consultant level and not devolved to junior doctors.

Follow-up for patients discharged home before being discharged from the ROP screening service has always been problematic. The Guideline suggests this should be the responsibility of the named neonatologist for each baby. However, wherever possible, screening should be completed prior to discharge.

Integrated care pathways

Integrated care pathway systems can be set up, preferably electronically, to identify to clinicians when the agreed Guideline has not been followed. This also provides an important strand of the clinical governance pathway and should identify any babies whose follow-up has stopped prior to discharge of the baby from the ophthalmologists.

Conclusion

The Guideline provides, where the literature exists, an evidence-based document covering all aspects of ROP screening and treatment. Utilising the revised ROP classification and new recommendations for treatment it highlights the importance of team work in implementing an effective screening programme. For the first time the Guideline introduces suggestions for the comfort of the babies during screening.

It must be remembered that although ROP is a highly important ophthalmic condition to screen for, largely because of its innately treatable nature, it is not the only ophthalmic challenge facing prematurely born infants. Extremely low birthweight (<1000g) infants are three times more likely to have a vision of less than 6/60 than those born at term[27] and low birthweight infants also have increased rates of treatable refractive errors and strabismus[28].

Acknowledgement

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The Guideline and its evidence base in full is available at www.rcpch.ac.uk, www.bapm.org and www.rcophth.ac.uk

Charity aids development of a mobile phone-sized fetal heart monitor

Trials are underway on a new heart rate monitor which could save the lives of hundreds of babies every year.

Action Medical Research, the charity that helped in the development of ultrasound scanning in pregnancy during the 1970s, has funded eight years of development work for the new monitor.

Each day, 10 babies are stillborn in the UK[1] – a figure which the Monica AN24 monitor, based on original research done by Drs Barrie Hayes-Gill, Jean Francois Pieri and John Crowe, aims to reduce.

The monitor offers obstetricians an unrivalled insight into the working of the unborn baby's heart and will be available to maternity units in the near future.

The trials at City Hospital Nottingham will monitor mothers who have previously had a stillbirth or have a condition that could threaten their unborn baby.

The mobile phone-sized device is small enough to be worn continuously for 24 hours and should release mothers from long-term stays in hospital. Action Medical Research hopes that, like ultrasound, it could eventually become a commonly used obstetric tool.

Existing methods to record babies' heart rates in pregnancy provide limited information and are too cumbersome and potentially hazardous to allow continuous, long-term monitoring.

Dr Terry Martin, Marketing Director for Monica Healthcare, the company that designed the final product, says: "A big challenge for us was to 'pick up' the unborn baby's heart beat clearly.

"The electrical reading from a baby's heart beat is so small compared to other electrical signals, including the mother's own heart beat, that it is very difficult to find. For mothers at risk of stillbirth, this device could give doctors a vital insight into the right time to induce delivery and so reduce the numbers of babies stillborn."

The device also offers clinicians information on the functioning of the maternal heart as well as important detail on how the fetus is lying within the womb.

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