Retinopathy of prematurity: clinical aspects

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There have been many major advances recently that have improved the identification and management of retinopathy of prematurity (ROP). This chapter describes the clinical features of ROP and then considers briefly the incidence and epidemiology of acute phase disease. This is followed by a discussion of the two ROP epidemics and ROP-induced disability in high, low and middle income countries, and how this has been impacted by treatment. The principles and specifics of screening for ROP are considered, focusing on certain topical issues such as whether one screening guideline suits all populations. Treatment has undergone several advances, so that now laser therapy has overtaken cryotherapy as the preferred mode of treatment, and treatment at an earlier stage is now being considered. Finally, the authors attempt to look into the future and wonder how the criteria for treatment will change, and whether innovations in ocular imaging will impact ROP screening in both high and middle income countries.

Introduction

The past 15 years have been an exciting period for retinopathy of prematurity (ROP) research and the fruits of this intensive activity have had a major impact on clinical practice world-wide. The advances in basic science are covered elsewhere by McCollm and Fleck, so here we will focus entirely on the clinical aspects of ROP, especially acute phase ROP.

The story starts with the publication of the International Classification of Retinopathy of Prematurity (ICROP) in 1984 \cite{1} and its modification in 1987 \cite{2}. This event initiated a wave of multicentre research, the results of which now constitute a major portion of the evidence base for current clinical practice world-wide.

Prior to 1988, the ophthalmologist had no role in either ROP prevention or treatment, so in many countries including the UK, neonatal screening was not considered essential and was not universally conducted. At that time a randomized, controlled trial, the 23 centre Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO–ROP Study) demonstrated \cite{3}, that cryotherapy significantly improved the anatomic and visual outcomes of babies with severe ROP. With a therapeutic intervention proven to be effective, screening for acute ROP that might require treatment became a priority and is now widely undertaken in many countries.

In this article we will consider ROP incidence and epidemiology, clinical features, screening, treatment and finally an attempt to glimpse into the future. There have been several recent reviews \cite{4-7} and the focus here will be on topics of current debate and special interest.

Terminology

A brief description of ROP and its terminology is appropriate at this juncture.

ROP is a condition confined to the immature retinal vascular system. The likelihood of developing retinopathy is related to the degree of vascular
development so that once the retina is fully vascularized the risk of developing ROP has passed. Vascularizing proceeds centrifugally from the optic disc, commencing at about 16 weeks of fetal life and is complete in the nasal retina by 32 weeks gestation age (GA) and by about 37 to 40 weeks GA in the temporal retina [8].

Thus, as retinal vascularization proceeds symmetrically from the optic disc to the ora serrata, there is an advancing circumferential border between vascular and avascular retina. It is within this border area that acute ROP develops. This predictable pattern of retinal vascularization was formally recognized by ICROP which divided the retina into progressive concentric zones. The location of ROP is described in terms of these arbitrarily defined ICROP zones (Fig. 1). The appearance of the disease at a rather consistent postmenstrual age (PMA), regardless of the elapsed time following preterm birth or subsequent neonatal events, suggests that the innate maturation process of the retina and its vessels is related to the timing of this disorder’s onset and progression [9–11].

### Describing ROP

ROP is described by four parameters (Figs 1–8):

1. **Severity by stage (1 to 5)**

ROP develops in the neonatal period and acute phase ROP is described by five stages. The specific characteristics of the various stages are described in the figures. Stages 1 and 2 are referred to as mild ROP as they often resolve without visually threatening ophthalmic sequelae.

Stage 3 ROP is the first ROP stage that presents a significant risk of poor structural or visual outcome and thus represents serious disease. Stage 3 ROP is commonly subdivided between the CRYO–ROP defined pre-threshold (moderate) ROP and threshold (severe) ROP.

Stage 4 ROP represents a partial retinal detachment, either peripherally (stage 4a) or centrally (stage 4b). Stage 5 ROP denotes a total retinal detachment. Obviously stage 4 and especially stage 5 usually result in some permanent visual impairment despite surgical intervention [12].

2. **Location**

As retinal blood vessels grow progressively across zone 1 through zone 3 (Fig. 1), the location of normal vascularization or ROP broadly reflects maturity and the progress of retinovascular development. Thus, the extremely immature baby whose retinal blood vessels are still within zone 1 at initial screening is at the greatest risk of the most severe disease [13]. For instance, incomplete vascularization in zone I carries a 54% risk of reaching threshold ROP while for zone II this is only 8% [14]. The larger baby whose retinal vessels have already grown into zone 3 by the initial exam has an extremely low risk of developing severe ROP, and when it does occur, it is likely to be mild, with a close to zero risk of visual impairment [13].

3. **Extent**

Thinking of the retinal periphery as a clock face, the extent of ROP around the retinal circumference is recorded in ‘clock hours’, one through twelve.

4. **‘Plus’ disease**

Being a vascular disorder, ROP severity is reflected by vascular engorgement and tortuosity of the mature feeder vessels, commencing close to the optic disc (posterior pole) and later extending in more severe disease forward to the iris. Eventually the vitreous becomes hazy. Signs of ‘plus’ disease may be superimposed on any ROP stage or rarely even as a precursor to ROP. Acknowledged as a critical sign of severe ROP [15] its presence is an important prognostic indicator and in the CRYO–ROP Study increased the chance of an unfavourable outcome (defined in this study as 20/200 or worse) from 3% to 62% for zone 2, stage 3 ROP identified at 33–34 weeks PMA [16].

**Prethreshold and threshold ROP**

Prethreshold ROP is the first form of severe ROP while ‘threshold’ ROP currently represents the
minimum severity of disease indicating the need for surgical intervention – both terms are defined later.

Figure 1. This figure shows the blood vessels extending from the optic disc (central smallest circle), first through retinal zone 1 towards zone 3. Acute ROP develops at the growing tips of the blood vessels. X marks the macula. There are no visible landmarks delineating zones, so that the radius of zone 1 is defined as the field contained within a single image of a 25 dioptre indirect lens, with the optic disc at one edge. Zone 2 extends to the retinal periphery in the nasal retina, but there are no defining landmarks in the temporal retina. Numbers on the periphery indicate clock hour and used to describe the circumferential extent of the ROP lesion.

Figure 2. Stage 1 ROP, a thin white line lying within the plane of the retina and separating the avascular (the extreme right) from the vascularized retinal regions. All pictures in this article taken used wide angle contact fundus camera.

Figure 3. Stages 1 and 2 (mild) ROP. ROP is represented here as a thin white line (stage 1), but towards its upper extent it increases in volume and extends out of the plane of the retina (stage 2). In many instances it can be difficult to differentiate stage 1 from 2.

Figure 4. Stage 3 ridge with extraretinal fibrovascular proliferation, sometimes disconnected from the ridge – here associated with a small haemorrhage.

Incidence and epidemiology

Acute phase ROP

Acute phase ROP incidence data has been published on many occasions, usually from single centres [17–21]. Many of these reports have serious flaws or inherent biases which prevent accurate conclusions that can be generalized [22]. There have been three prospectively designed epidemiological studies [23–25], one which was undertaken after the introduction of cryotherapy [25].
Detailed analysis of incidence data is not a particularly rewarding exercise for this article and the reader is directed therefore to reviews [4–6]. Despite some differences between reports, it is agreed that ROP incidence and severity rise with increasing prematurity. The most reliable statistics for moderate and severe disease come from the large, prospective, randomized, multicentre CRYO–ROP trial [3]. The national history portion of that study [11] reported incidences that were based on large numbers of patients, well-trained, validated, and consistent examiners, using a rigorously designed protocol. The incidence of stage 3 ROP in babies under 1251 g was reported as 18% and for threshold as 6% [11]. Zone I ROP affected only 1.7% of babies, but with over half progressing to stage 3 [13] its propensity to reach threshold ROP was high [16].

The more recently conducted LIGHT–ROP multicenter study [26], with similar design attributes confirmed the basically stable rates of ROP incidence and severity within birthweight categories.

Figure 5. Stage 3 ROP – mild. The ridge can be seen which in its middle portion thickens to become stage 3. Posterior to the stage 3 are several small isolated neovascular tufts – popcorn – which may coalesce to form stage 3. Note the retinal arterioles are tortuous compared to those in Figs 1 and 2.

Figure 6. Plus disease. The first sign is congestion of the posterior pole veins. In this figure plus is asymmetrical as was the stage 3 ROP. The engorged vessels ‘point to’ the active ROP. Venous engorgement and arteriolar tortuosity are associations of severe disease or powerful indicators that severe ROP is likely to develop.

Figure 7. Plus disease. Persistence of the transient tunica vasculosa lentis, a sign that ROP is severe. A sign indicating greater ROP severity than vascular engorgement of the retinal blood vessels.

Figure 8. Plus disease. Persistence of the tunica vasculosa lentis – view as seen through a direct ophthalmoscope.
Even with such statistically powerful studies as CRYO–ROP and LIGHT–ROP, important caveats remain. Comparisons to other populations or studies must consider such factors as racial differences [23,27] and technique and frequency of examinations or disease reporting definitions. The last two are more likely to affect the incidence figures of mild ROP, especially as signs are subtle and transient, which is why the diagnostic criteria for confirmed stage 1 ROP differed between the CRYO–ROP [3] and LIGHT–ROP [26] Studies. The relevance of these factors will also be apparent when ROP in populations across the world is considered. Neonatal practice has also been implicated as a factor for ROP development [28,30].

Another factor is the categorization of liveborn, stillborn and abortion that differs between centres [28]. Thus, one English city had a higher than predicted death rate but a low ROP rate, probably due to the recording, in this city, as a live birth even the most immature live-born infants [29]. The city with the highest ROP incidence had a death rate lower than predicted by the CRIB score [29].

Medical advances have improved the survival of extremely premature babies in the intervening 10–15 years since many of the incidence data presented above were published. It has been suggested recently that the incidence of acute phase ROP is declining [31,32] and while these findings could represent a general trend, coming as they do from single centres, they could also represent a statistical regression to the mean [22]. In 1999 Hussain, also reporting from a single NICU between the years 1989 to 1997 reported lower incidence rate than CRYO–ROP, but observed no sustained trend across this period [33]. For all the reasons cited, trying to tease out, from single-centre studies, secular changes in ROP incidence is fraught with difficulty and mindful of the differing populations and standards of care (see below), the results of such studies inevitably have limited applicability.

**ROP-Induced disability**

Mild acute-phase disease spontaneously resolves without visual sequelae and it is now time to review the situation of severe ROP that progresses to cicatricial disease and its consequent visual disability.

Knowledge of this topic on a worldwide basis has recently advanced significantly, mainly due to

the work of Gilbert and colleagues [34]. This has not only provided epidemiological data, but also a glimpse into the fundamental relationship between neonatal care and ROP causation. Broadly, there are three health-socio-economic populations, in countries that have high, middle or low wealth.

**High-income countries**

In the UK, US, Australia, Scandinavia and other countries, high wealth and consequent advanced technology permit health care of the highest quality to the entire at risk population. Thus, resources are sufficient to provide optimal neonatal intensive care support for the extremely immature premature baby. In these countries the prevalence of ROP-induced disability constitutes around 5–8% of childhood vision impairment [35–37] and is confined mainly to babies below 1000 g and almost entirely to those below 1500 g birthweight. In high-wealth countries ROP-related vision impairment is more likely than not to be associated with multiple disability [36,38,39].

Survival of the most immature preterm baby has increased, but disappointingly the proportion of disability overall in this population has remained constant [40], or even increased [41,42].

**Middle-income countries**

In these countries, expansion of neonatal services has permitted the increased survival of preterm babies, but limited health resources do not permit the appropriate standard of neonatal and especially ophthalmologic care for premature babies. In these countries, such as several in Latin America, Eastern Europe and Thailand, severe ROP affects preterm babies with a wider range of birthweights and gestational ages and constitutes up to 39% of visually impaired children [34]. Thus babies over 1500 g and even over 2000 g birthweight are at risk, babies who are hardly at risk in countries with optimum intensive care. As these data come from surveys of schools for visually impaired children, children who are multiply disabled and also have a vision impairment are likely to be underrepresented.

**Low-income countries**

In these countries (e.g. Malawi, Kenya, Eritrea, Sri Lanka, Albania) health care provision is low and
they lack the facilities to support the survival of babies born prematurely. Therefore, few preterm babies survive to develop severe ROP and in the countries cited no case of blindness due to ROP was seen [34].

Impact of treatment on disability

Following the widespread adoption of treatment for severe ROP since 1988, it is important to inquire whether this change of practice has reduced ROP-induced disability. Two articles [41,42] report an increase in ROP disability, but because of their temporal proximity to the widespread introduction of treatment it is not possible to determine the ophthalmic care these babies received. In contrast, three studies [44–46] (two geographically-based [44,45]), reported a treatment-induced decrease in disability. One study demonstrated that the reduction could be attributed to treatment and not a fall in the incidence of ROP that required treatment [46].

The most robust evidence of reduced disability both with respect to frequency and severity comes from the 10-year outcome of the CRYO–ROP Study [43]. This confirms the long term beneficial effect of cryotherapy: favourable visual function (better than 20/200) occurred in 55.6% treated compared to 37.9% control eyes, and fewer treated eyes were classified as blind: 32.7% treated and 49.8% control eyes. Treated eyes were more stable and less likely to develop retinal detachment [43].

The ROP epidemics

The literature contains many references to two ROP epidemics. The first occurred in the 10 to 15 years following 1942 and was due mainly to high, unrestricted and unmonitored, oxygen administration. The excessive amounts of oxygen administered at that time almost certainly swamped all other ROP risk factors, even the effect of immaturity, so that in this era blinding ROP affected a wide birthweight range of premature babies. Because the survival of babies under 1000 g birthweight in the 1940s was under 10%, most of those babies blinded at this time had a birthweight exceeding 1000 g.

The second ‘epidemic’ commenced slowly in the 1970s and continues to the present time. Advances in neonatal intensive care, including the meticulous administration and monitoring of oxygen administration, have largely eliminated the risk of severe ROP for the more mature preterm babies, so that nowadays severe ROP is mostly confined to babies of birthweight under 1000 g. Consequently the second epidemic reflects mainly the increased survival of extremely premature babies.

The situation described so far presents the two epidemics as discrete entities – this oversimplifies a complex situation and loses the sense of ROP causation. While in high income countries, increased survival is the main ROP factor, standard of care still contributes to its development [29,47]. In middle income countries the prevailing health care environment contains elements of both epidemics, namely increased survival but with limited resources that do not permit the highest quality of neonatal care.

Screening for ROP

Mild ROP (stages 1 and 2) does not lead to major sequelae, and would probably not therefore merit screening per se. Neither would stage 4 and 5 ROP, because however anatomically successful is surgical intervention, the functional outlook is dismal [12]. For these reasons, the focus of ROP screening is to identify stage 3 ROP, for it is at a subdivision of this stage (threshold ROP) that treatment is undertaken. Evolving treatment patterns are still highly likely to be limited to different subdivisions of stage 3.

General considerations

Before discussing specific screening guidelines it is appropriate to set the scene with a few general points.

ROP screening examination and the baby

Prior to the examination, the pupils are dilated and the examination is performed by indirect ophthalmoscopy using a 20, 25 or 28 dioptre lens. It is helpful to use an eyelid speculum and scleral depressor to rotate the eye into the appropriate position. The eye examination is stressful for babies, may cause bradycardia, and this can be reduced by
nitting [48,49]. Slow gastric emptying following mydriasis has also been reported on one occasion [50].

Age at onset and rate of progression

While the propensity of a baby to develop severe ROP is influenced by many factors such as the degree of prematurity and neonatal events, the time at which it develops appears to be largely independent of these events [9,10,11]. This knowledge has proved useful in the design of ROP screening guidelines for it is known that most babies – whatever the degree of immaturity and illnesses – develop ROP at a time which can be predetermined to a significant degree, and which progresses according to PMA. In the CRYO–ROP Study treatment was usually required between 37–39 weeks PMA age (mean 37.7 weeks, range, 32–50 weeks [51], although Subhani et al. [52] recently reported threshold ROP developing as early as 31 weeks PMA in babies under 1000 g birthweight.

Site of onset

At its onset, ROP involves the circumferential retina within the horizontal regions of the retina, frequently first the nasal retina in the most immature, with vertical regions only being involved when the other parts are also affected [10].

Location by zone

Increasing (more peripheral) zone is an important predictor of decreasing risk. Zone I ROP is high risk disease; zone II has moderate risk; and zone III has very low risk. By ICROP convention the zone of disease or incomplete vascularization is assigned on each examination. This not only allows assessment of disease risk at the time of the exam, but also has prognostic value when assessing disease progression over serial exams.

The location of disease is not static. Over the course of time zone I disease may become zone II and zone II disease may move into zone III. Although this phenomenon is well recognized, it is not easily explained. Ocular growth may account for zone changes, but other processes may be at work.

Clearly disease that was initially more central (zones I or II) that becomes more peripheral (zones II or III) carries less risk. But, it is more complex than that. Zone III ROP that originated in zone III has a poor outcome risk of about one in 500. But zone III ROP that was initially zone II ROP has a 2% risk of a poor outcome (REPKA) [53]. The clinical significance of these facts is that there is prognostic value in screening exams that detect ROP early and observe disease progression serially.

Symmetry

Acute phase ROP exhibits a high degree of symmetry, infrequently differing by more than one stage. In contrast, the residua are frequently asymmetric [10,54].

Current clinical guidelines

Recommendations for screening have been produced in several countries and along with treatment have been shown to be cost-effective. To facilitate understanding of the concepts underpinning screening, here we will compare the major components of two sample guidelines: UK, 1995 [55] and USA, 2001 [56]. When there is concordance between the two guidelines the countries are not cited in the text.

Goal of screening

The purpose of screening is to identify preterm infants that require treatment for ROP, while minimizing the number of stressful examinations.

Infants to be screened

It is recommended in the US that screening should include all infants with a birthweight of less than 1500 g or with a gestational age of less than 29 weeks, and in the UK all of birthweight less than 1501 g and less than 32 weeks gestational age. Infants between 1500 and 2000 g who, due to their unstable clinical course, are considered by the
neonatologist to be at risk of ROP should also be examined in the US while in the UK the option for screening larger infants is left open. The recommendations from the two countries are very similar as there are relatively few babies between 28 and 31 weeks GA who are not under 1501 g birthweight.

Examination protocol

Commencement of screening

The initial exam is recommended at 4 to 6 weeks postnatal age, or within 31 and 33 weeks PMA, whichever is later, in the US; and at 6–7 weeks postnatal age in the UK. In the US, it is acknowledged that the national recommendations may be fine-tuned to meet local incidences and needs. No such flexibility is offered in the UK.

Frequency of follow-up examinations

In the US this can be determined by the examining ophthalmologist, but those infants with ROP that may soon progress to threshold should be examined at least weekly, while those with less severe ROP may be examined fortnightly. In the UK, weekly or fortnightly examinations are recommended unless severe ROP is present, in which case more frequent review is encouraged. The UK guidelines recommend the completion of the ROP screening programme while the baby is in hospital, to minimize inconvenience to the family. In the UK this can be achieved for over 90% babies. This recognizes the problems of obtaining good compliance with follow-up arrangements after discharge [57]. Weekly screening examinations, when close to discharge, improves the likelihood of completing the screening programme in hospital. This reduces the necessity for outpatient appointments, and the infant with potentially blinding ROP ‘slipping through the net’. In the US earlier discharge is becoming standard, necessitating outpatient examinations in a large percentage of infants.

Completion of screening programme

In the absence of any ROP, screening can cease when the retinal vessels have grown into zone III.

Treatment

Infants reaching threshold should be treated within 72 hours of this diagnosis.

Communicating with parents

Parents of babies with ROP should be kept up to date with progress.

Responsibilities

In the US it is recognized that specific local issues need to be incorporated into the guidelines and that the screening programme and responsibilities should be drawn up jointly by local neonatology and ophthalmology services. Should responsibility for follow-up after hospital discharge devolve to parents (this would not happen in the UK), oral and written information about the potential severity of the condition must be transmitted to the parents. ROP screening is difficult and the need for it to be undertaken by ophthalmologists with interest and knowledge of this area is acknowledged [55,56].

Comment

There is considerable concordance between US and UK guidelines although the latter are rather more prescriptive in some respects. ROP screening and treatment have been shown to be cost-effective [58,59].

Screening – issues for debate

The timely diagnosis and treatment of babies with severe ROP have improved their long term visual functions. Nevertheless, it is only natural that all aspects of ROP screening and treatment should be frequently questioned to ensure that they remain valid in the light of advances of neonatal and ophthalmic care.

Goal of screening

The first priority of screening is to identify the baby who requires treatment, at the appropriate point in the disease progression. However, there is
a trend for treatment to include babies at a milder stage 3 ROP than ‘threshold’ as defined in the CRYO–ROP Study [3]. As an aside, as stage 3 ROP is associated with such a high incidence of strabismus, myopia and vision deficits it could be argued that these babies require long-term ophthalmic surveillance anyway. Thus, for the purpose of the ensuing discussion, the focus of screening will not be to diagnose threshold ROP, but to identify any stage 3 ROP.

**Which babies to screen?**

Several studies have expressed concern that current ROP screening guidelines in both the US and UK include larger and more mature babies who are not at risk of developing ROP that requires treatment. Thus, a Canadian study reported an absence of serious ROP in more than 16 000 babies over 1200 g [60] whilst in the UK no baby developed stages 3 >1250 g or >29 weeks [61,62]. Using birthweight and gestational age together has the advantage over using one parameter alone in that it brings in the outliers and so reduces the number of babies that need to be screened. For instance, the criteria of 1250 g and ≤29 weeks GA, would encompass a baby of 1375 g and 29 weeks GA, and another of 930 g and 31 weeks [62]. Hutchinson et al. [63] and Wright et al. [64] both reported stage 3 ROP in babies exceeding 1250 g and 31 weeks GA but whether by combining BW and GA they would have fallen within 1250 g or 29 weeks GA is unknown.

**Time of initial examination**

Subhani et al. [52] reported that the onset of threshold ROP in babies <1000 g ranged from 31 to 40 weeks PMA and recommended that screening commences at 5–6 weeks in these very small babies. Reynolds et al., in their LIGHT–ROP Trial reported in 1998 [26,65], developed an algorithm for initial screening examinations based on the pathophysiological data that younger babies take longer to develop serious ROP while older babies develop this sooner, i.e. that ROP onset and progression correlates very strongly with PMA or retinal maturation. Their algorithm allowed for the fewest examinations while still identifying all severe ROP at the appropriate point. Hutchinson et al. [63] suggested using both postnatal age and PMA together, so that screening starts at 7 week postnatal age or 34 weeks PMA whichever is shorter – i.e. did not commence too early for the extremely premature baby, but in time for the older infant.

**Can fewer babies be screened for ROP?**

A definite answer to this question cannot be given here, although there is firm evidence that the incidence of severe ROP over 1000 g and 29 weeks GA is very low in high income countries. However, more local and national epidemiological data are required before guidelines are changed. The Canadian experience [60] is compelling for placing the upper level for screening at 1200 g in this country, but clearly if this were applied to the US and UK some babies with severe ROP would be missed [33,62–64].

**Does one screening guideline suit all?**

The current screening criteria of 1500 g and 28 weeks GA include virtually every baby in high-income countries. The exception is the large baby who would not be identified by any current guideline, for instance the Canadian baby of 1785 g [60]. It will be interesting to see how guidelines are amended in the future to reduce the number of babies to be screened.

It is obvious and critical to emphasize that our two models, the UK and US recommendations for screening, are not directly transferable to other populations such as the middle-income countries where babies with a wider range of birthweights and gestational ages are at risk of severe disease. For these countries, accurate screening guidelines can only be derived when ROP incidences in these populations are determined by local and preferably national audit.

**ROP treatment**

This section will focus entirely on treatment of severe ROP by cryo or laser. Prophylactic measures are considered by McColm and Fleck in their chapter in this issue.

**Indications**

The CRYO–ROP Study [3] divided all stage 3 disease into two categories: pre-threshold (or
moderate ROP) and threshold (or severe ROP). Any stage 3 less than threshold was considered pre-threshold. Threshold ROP defined the minimal disease severity that required cryotherapy. Thus threshold ROP was defined as:

‘At least 5 continuous or 8 cumulative clock hours of stage 3 ROP in zones I and II, in the presence of “plus” disease.’

This term was based on consensus opinion which considered that the risk of blindness at this stage, if untreated, is around 50% [3]. The 10-year results of CRYO–ROP Study [43] demonstrate the long-term benefit of treatment, but also that intervention is no panacea. Thus, there is now a trend towards earlier treatment, especially for zone I disease [65], and in the STOP–ROP Trial [67] ‘threshold’ was redefined, as:

**Zone II:** Presence of dilatation/tortuosity in at least 2 posterior pole quadrants and stage 3 ROP for at least 5 continuous or 8 cumulative clock hours.

**Zone I:** Any stage of ROP with posterior pole dilatation/tortuosity in at least 2 quadrants, or stage 3 ROP, with or without plus disease.

It is anticipated that in the near future treatment criteria may change to milder degrees of stage 3 ROP, but this has to be balanced against the risk of unnecessarily treating babies whose ROP would have resolved spontaneously. The STOP–ROP criteria [67] are a sensible compromise, for they recognize that zone I ROP is severe, and in the CRYO–ROP Study had an unfavourable outcome in 78% [51]. However, it also has a different appearance than ROP in zone II and can be difficult to assess, thus making intervention dependent on a more difficult clinical judgment.

The definitive answer on whether intervention earlier in the course of ROP is efficacious should be forthcoming from a National Institutes of Health sponsored multicenter early treatment trial, ET–ROP. This randomized trial has been enrolling patients since 2000 [68].

### Mode of treatment

In addition to cryotherapy, technological advances now permit ROP treatment to be delivered by laser (diode is used more frequently than argon laser). The latter can be delivered by either transpupillary [66,69–79] or by transcleral methods [80,81]. Transpupillary laser involves the ophthalmologist, via an indirect ophthalmoscope, directing the laser beam by a target light on to specific areas of the retina. Transscleral laser employs a probe (not too dissimilar to the cryoprobe) which is applied to the external scleral surface. The location of the probe on the exterior of the eye is seen as an indentation of the retina which is viewed via an indirect ophthalmoscope. Thus, treatment can be delivered precisely, and is seen as retinal blanching – the response seen in all ROP treatment modalities – cryo or laser.

For many years, both cryo and laser have been used to ablate the retina to treat a number of retinal conditions of children and adults, and sometimes the two modalities are used almost interchangeably. There has not been a randomized controlled trial to compare laser and cryo, but following the success of the CRYO–ROP Study it is unlikely that this would receive a high priority. With the advent of new laser delivery systems, notably through the indirect ophthalmoscope, there has been a shift to using this modality in preference to cryotherapy. Thus, in the STOP–ROP Trial [67] undertaken a decade after the CRYO–ROP Study, 93% babies were treated by laser (73% diode and 20% argon) and by cryotherapy alone in only 7%.

### Treatment outcome

This has already been partially covered. Both cryo and laser are effective [65,68–80], although some studies report cryo and laser to be equally effective [79], and a number of studies report laser to be associated with a better outcome with respect to visual acuity and refractive status [74,78]. The debate about whether laser is associated with less myopia than cryo is unresolved, although the magnitude of any difference is unlikely to be great. The complex relationship between myopia and prematurity per se, mild ROP, and severe ROP and its treatment modality is unresolved [73,74,79,82,83], but recent evidence does not support the concept that cryotherapy increases myopia [84].

Both cryotherapy and laser have advantages and disadvantages. Laser is ideal for very posterior disease, which can be difficult to reach with the cryotherapy probe, while laser therapy cannot be used in presence of massive iris rubeosis or vitreous blood, and can be rarely complicated by corneal burns and cataract.
The future two decades have seen tremendous improvement in the identification and treatment of ROP. But, there is still some way to go, and in this final section we look at a few directions for the future.

Ocular imaging

The recent development of contact wide-field digital retinal imaging (e.g. RetCam 120) has opened up new opportunities for ROP service and research (Figs 2–12, 14, 15). This technology by which Figs 2–12, 14, 15 were obtained, offers an advantage in that: the examination can be performed by a professional other than an ophthalmologist, although this has yet to be fully evaluated. Roth et al. [85] compared images obtained by RetCam120 contact digital fundus camera by an ophthalmic photographer, with the findings from indirect ophthalmological examination. The positive predicted value of RetCam120 was excellent at 96.6%, but there were 12 false-negative and 2 false-positive results, and discrepancies regarding ‘plus’ disease. Five examinations revealed stage 3 by one technique only, however, none of these

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**Figure 9.** Stage 3 ROP, image obtained a few minutes after laser treatment. Stage 3 can be seen in the upper half of the picture. Treatment is applied to the avascular retina anterior to the stage 3 and not to the lesion itself.

**Figure 10.** Severe zone 1 ROP, imaged a few minutes after laser treatments. The active lesion cannot be clearly distinguished. Note the plus disease – vascular engorgement, tortuosity and haemorrhage. Note how much closer the lesion is to the optic disc in zone 1 ROP.

**Figure 11.** Slight temporal dragging of the retinal vessels, often incorrectly referred to as a dragged optic disc. This lateral traction of the retina may cause displacement of the macula and so impair visual acuity. Note cryotherapy scar at top.

**Figure 12.** Stage 5 ROP. Extensive retinal fibrosis and detachment. This untreatable stage developed within a few weeks of term, demonstrating that the window of opportunity for successful treatment is very short.
discrepancies affected the decision to treat. Teaching at the cot-side and elsewhere is facilitated, so reducing the need for additional stressful examinations, with the benefit that the images can be used to keep both parents and other NICU staff informed as to an infant’s ROP status.

Through new generation imaging, hopefully the days of hand sketches will soon be past and data will become more robust. Captured images, from poorly, fragile infants, requiring urgent assessment, may be transmitted electronically without degradation via the internet and stored on central servers where they are available for local assessment and through telemedicine also to remote expert opinion at any time [86].

Objective recording of neonatal examinations will permit the natural history of ROP to be studied in a detail hitherto not possible, and the recording of both pre- and post-treatment appearances holds promise for research and clinical trials. Advanced image processing will hopefully enable plus disease and other features of ROP to be quantified.

**Screening**

Earlier in this article we debated the need to fine-tune ROP screening guidelines, but we have not addressed the human resource issue. A recent UK national audit showed that of 8200 babies screened annually (about 1–8 examinations per baby), less than 2% of these required treatment (numbers were similar for the preceding two years [87]. With such a low treatment yield this represents a massive ‘funnel effect’ and one could reasonably question whether this is an appropriate use of expensive ophthalmic expertise. The challenge is far greater in middle-income countries where expertise is in sparse supply and yet there are more babies who need to be screened and treated.

It is appropriate to develop further the studies of Schwartz et al. [86] and Roth et al. [85] using new ocular imaging to explore the possibilities of other professionals performing ROP screening.

**Treatment**

Advances in our understanding of the pathogenesis of retinopathy as described by McColm and Fleck...
offer considerable hope for ROP prophylaxis. For those babies who still develop severe disease the Multicenter Study of Early Treatment for Retinopathy of prematurity (ETROP [68]) holds much promise and hopefully will help us understand and reduce the sequelae of ROP.

Service organization

A recent report [86] of a national UK audit shows several aspects of ROP screening and treatment services require improvement. In essence reducing the number of ophthalmologists that participate in screening and treatment would increase skills, confidence and the ability to recognize and treat severe ROP. Of course health service organization differs from country to country but critical mass is an important principal to the improvement of any service. Ziakis et al. [88] have recently demonstrated that the reorganization of ROP screening services improves compliance with guidelines.

Conclusion

Recently there have been tremendous strides in the neonatal and ophthalmic management of the preterm baby. There is still much to do, but hopefully by harnessing new technology and breaking down professional barriers, some of the remaining challenges can be overcome.

References

56 American Academy of Pediatrics, American Association for Pediatric Ophthalmology and Strabismus, American
Retinopathy of prematurity


