

## ARTICLE



# The Royal College of Paediatrics and Child Health Retinopathy of Prematurity Screening Guidelines (2022): a series of treated infants falling outside the updated criteria

Simranjeet Aulakh<sup>1</sup>, Anne Cees Houtman<sup>2</sup>, Dinesh Rathod<sup>3</sup>, Susmito Biswas<sup>4</sup>, Eibhlin McLoone<sup>5</sup>, Ayad E. Shafiq<sup>6</sup>, Mahmoud M. Nassar<sup>6</sup>, Alan J. Connor<sup>6</sup> and Roxane J. Hillier<sup>6,7</sup>✉

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**BACKGROUND/OBJECTIVES:** Screening for retinopathy of prematurity (ROP) is a core healthcare intervention in premature babies to avoid preventable sight loss. A variety of screening criteria are in place globally for this purpose. The Royal College of Paediatrics and Child Health recently updated the United Kingdom ROP screening guidelines (March 2022). A key change was the reduction in the gestational age (GA) to warrant retinal screening (from 32 to 31 weeks).

**SUBJECTS/METHODS:** In the course of informal national surveillance during guideline development (2017–2022) and soon after, babies under our care falling outside the updated screening criteria who underwent treatment for ROP were identified. A retrospective case review was carried out.

**RESULTS:** Six babies were identified as having undergone screening and treatment, prior to implementation of the new guidance. Screening and treatment would have been forfeited as per the March 2022 guidelines. All six had numerous systemic risk factors for developing ROP. Specifically, all had documented poor postnatal weight gain.

**CONCLUSIONS:** We present this case series to bring forth an urgent discussion amongst key stakeholders as to whether the new guidance, as it stands, is safe and fit for purpose.

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## INTRODUCTION

Retinopathy of prematurity (ROP) is an important cause of childhood blindness. Various guidelines for timely retinal screening have been developed across global healthcare systems to identify premature babies at risk of severe visual impairment. Previous United Kingdom (UK) national guidance (2008) stated that infants less than 32 weeks gestational age (GA) or less than 1501 g birth weight (BW) should be screened for ROP [1]. However, updated guidelines released in March 2022 by The Royal College of Paediatrics and Child Health, endorsed by the Royal College of Ophthalmologists, state that only infants less than 31 weeks GA or less than 1501 g BW require screening. The new guidelines state that infants born before 31 weeks GA should be examined between 31 + 0 and 31 + 6 weeks postmenstrual age (PMA) or at 4 completed weeks postnatal age (PNA), whichever is later. Infants born at or after 31 weeks GA with BW less than 1501 g should be examined at 36 weeks PMA or 4 completed weeks PNA, whichever is sooner [2].

## METHODS

Informal national surveillance amongst members of a national collaborative ROP special interest group took place during the period of guideline

development (2017–2022) and soon after. A retrospective case record review was performed for infants born in the UK with GA greater than 31 weeks and BW greater than 1500 g, identified as having undergone treatment for ROP between March 2017 and March 2023. As per the updated UK guidelines, these babies would have been exempt from screening.

## RESULTS

### Case 1

A male twin of white British ethnicity, born at 31 + 4 weeks GA with BW 2000 g, had respiratory failure and was diagnosed with chronic lung disease at 36 weeks PMA. There was a history of twin-to-twin transfusion syndrome with intra-uterine foetal demise of twin 2. On discharge, the baby was oxygen-dependent and found to have right frontal polymicrogyria. The first retinal examination was carried out at 37 weeks. There were 6 non-contiguous clock hours of stage 3, zone 2 ROP (no plus) in the right eye and 8 contiguous clock hours of stage 3, zone 2 ROP (no plus) in the left eye. A subsequent examination 4 days later revealed 6 non-contiguous clock hours of stage 3 ROP (no plus) in the right eye and 8 contiguous clock hours stage 3 ROP (with plus) in the left eye, for which bilateral laser treatment was undertaken at 37 + 5 weeks PMA.

<sup>1</sup>County Durham and Darlington NHS Foundation Trust, Darlington, UK. <sup>2</sup>Royal Hospital for Children, NHS Greater Glasgow and Clyde, Glasgow, UK. <sup>3</sup>Swansea Bay University Health Board, Port Talbot, UK. <sup>4</sup>Manchester Royal Eye Hospital, Manchester University NHS Foundation Trust, Manchester, UK. <sup>5</sup>Royal Victoria Hospital, Belfast Trust and Social Care Trust, Belfast, UK. <sup>6</sup>Newcastle Eye Centre, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, UK. <sup>7</sup>Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK. ✉email: [roxane.hillier@nhs.net](mailto:roxane.hillier@nhs.net)

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**Case 2**

A Caucasian male was born at GA 31 + 2 weeks with BW 1774 g. Maternal steroids were given prior to delivery. The baby had RDS for which surfactant was given, and congenital hydrocephalus with multiple intra-ventricular haemorrhages (grades 1 and 2). He developed microbiologically confirmed methicillin-resistant *Staphylococcus aureus* (MRSA) sepsis requiring treatment and platelet transfusion. The baby developed bilateral stage 3, zone 3 ROP (with plus) that was treated with 180° of temporal laser at 39 + 5 weeks PMA.

**Case 3**

A white British male, born at 31 + 1 weeks GA with BW 2771 g, developed bilateral aggressive posterior ROP (AP-ROP) (Fig. 1A, B). He was treated with intravitreal bevacizumab 0.5 mg injections bilaterally. A large congenital solitary renal cyst was noted antenatally. This cyst was drained antenatally and again at birth. The infant's weight reduced to 1950 g at one week post drainage, and as such the true BW for this baby was likely confounded by the weight of the cyst. The child had RDS with polycythaemia neonatorum and required intensive care and high-dependency unit admission for 13 days, during which high-flow oxygen was given. The baby also required intravenous antibiotics for suspected sepsis.

**Case 4**

A white British female was born at 31 + 5 weeks with BW 1659 g. The baby developed respiratory distress syndrome (RDS) for which surfactant was given. She required intubation for pneumothorax and received high-flow oxygen until day 62. At initial examination, there was stage 3, zone 2 ROP (pre-plus) in the right eye with stage 2, zone 2 ROP (pre-plus) and pre-retinal haemorrhage in the left eye. There was subsequent progression to 4 clock hours stage 3 ROP (with plus) in the right eye (Fig. 1C, D). Both eyes were lasered at 42 weeks PMA.

**Case 5**

A white British male twin was born at 31 + 4 weeks GA with BW 1680 g. The baby developed RDS for which surfactant was given

and required continuous positive airway pressure (CPAP) for 3 days. There was evidence of stage 3, anterior zone 2 ROP in one clock hour in the right eye at initial screening. This progressed to 2–3 clock hours of stage 3 in the right eye, with the development of one clock hour of stage 3, anterior zone 2 ROP in the left eye. No plus disease was recorded. The baby was treated with laser bilaterally at 42 + 2 weeks PMA, in view of rapid progression and history of RDS. It is important to point out that this case had the most stable neonatal course of those in this series. Although type 2 ROP developed, this infant's treatment was arguably initiated with the least convincing clinical indications.

**Case 6**

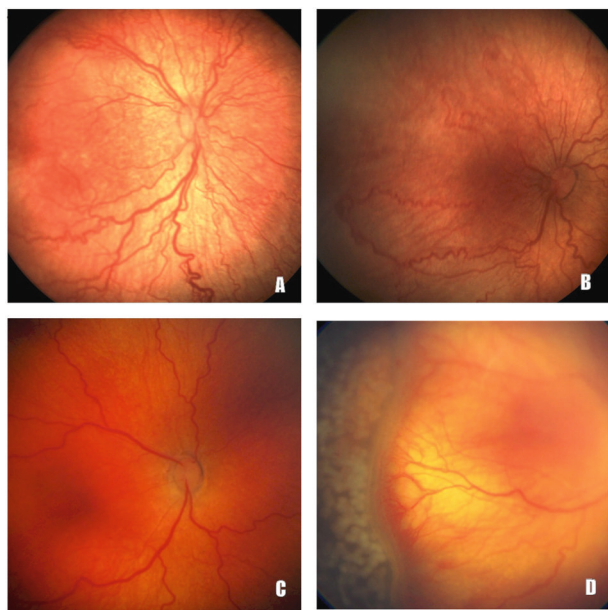
A Caucasian triplet male was born at 31 + 3 weeks with BW 1560 g. There was evidence of intra-uterine growth restriction which required planned early caesarean section. The mother received steroids prior to delivery. At birth, the baby developed RDS, which resolved with oxygen administered via CPAP and no surfactant was required. The baby received prophylactic antibiotics, which were discontinued once sepsis was excluded. He went on to develop stage 3, zone 3 ROP (with plus) bilaterally, requiring laser at 41 + 4 weeks PMA.

**DISCUSSION**

It is timely to consider whether national implementation of the recently updated UK ROP guidelines might result in failure to identify a subgroup of infants with sight-threatening disease. As a group of clinicians with extensive combined experience in the management of ROP, we feel that we must bring these cases to light. There is tangible merit in endeavours to narrow the screening criteria, such as reduced healthcare burden and screening-associated infant morbidity. It is therefore important to consider the guideline development process that led to the update. A prospective national population-based survey from 1 December 2013 to 30 November 2014 was carried out to determine the incidence of ROP requiring treatment. All paediatric ophthalmologists providing screening and/or treatment for ROP in the UK were asked to report any baby requiring any form of treatment for ROP. A total of 327 infants were reported. Infants requiring treatment for ROP had a median GA and BW of 25 weeks and 706 g respectively. No treated infant was over 32 weeks GA and only 1 weighed over 1500 g [3]. Simultaneously, the total number of premature babies with BW less than 1500 g was obtained from the Office of National Statistics of England and Wales for the same time period time period ( $n = 8112$ ). Based on this, the incidence of treatment for ROP amongst screened babies was deemed to be 4% (95% CI 3.6%–4.5%) [4]. In a subsequent analysis, the authors deduced that implementation of the updated guidelines would reduce the number of babies requiring screening in the UK from 9638 to 8428 annually (a reduction of 12.6%) [3].

The incidence of ROP is largely dependent on the level of postnatal care available in a given healthcare system, making the survival of premature babies more or less likely. Thus, the guidelines for ROP screening differ widely globally. Guidelines put forth by the American Academy of Pediatrics for ROP screening state that infants with a GA  $\leq 30$  weeks or BW  $\leq 1500$  g and infants with GA  $> 30$  weeks or BW 1500–2000 g with an unstable clinical course should be screened for ROP [5]. In India, GA  $\leq 34$  weeks and/or BW  $\leq 1750$  g warrant ROP screening. Babies with GA between 34–36 weeks or BW between 1750–2000 g with an unstable neonatal course are also screened [6]. The striking difference between these guidelines and those of the UK is the incorporation of neonatal systemic well-being indicators in the former.

There are several known risk factors for the development of ROP; GA and BW are identified as the most important, and thus most global guidelines hinge on these. However, numerous studies have



**Fig. 1 Fundal photographs (obtained on the day of treatment).** **A** Case 3; right eye AP-ROP. **B** Case 3; left eye AP-ROP. **C** Case 4; right eye, plus disease. **D** Case 4; right eye stage 3, mid zone 2 (immediately post laser treatment).

identified additional risk factors such as severe RDS, bronchopulmonary dysplasia, mechanical ventilation, surfactant treatment, anaemia, neonatal sepsis, thrombocytopenia, multiple blood transfusions, multiple gestations, intra-ventricular haemorrhage and ethnicity [4, 7, 8]. Tables 1 and 2 summarise the clinical features and risk factors present in our cases. There was no history of coronavirus infection in the mother or infant in any of baby born during the COVID-19 pandemic. Biomarkers can also be utilised for risk stratification. Insulin-like growth factor 1 levels predict the risk of developing ROP, and the weight gain of a newborn is also predictive of ROP risk [7, 9, 10]. WINROP is an algorithm that combines GA, BW, postnatal weight gain and IGF-1 to predict sight-threatening ROP risk [7, 9, 10]. More recently, the Postnatal Growth and Retinopathy of Prematurity Screening Criteria (G-ROP) have been validated in several populations around the world [11]. Criteria to screen include GA < 28 weeks, BW < 1051 g, postnatal

weight gain (<120 g across days 10–19, <180 g across days 20–29 and/or <170 g across days 30–39) and hydrocephalus (the latter was included as a potential confounder in terms of non-physiological weight gain). If any one of these criteria is present, then ROP screening is warranted. Prospective validation of G-ROP in 11,463 infants in North America and Canada found 100% sensitivity for type 1 ROP with a 32.5% reduction in the need for examination [12].

To determine whether the incorporation of postnatal weight gain criteria might enhance the sensitivity of the new UK guidance, we endeavoured to apply G-ROP study weight gain criteria to our cohort (Table 3). Where the available data was not recorded in line with the precise corresponding time range used in G-ROP, the closest range was used. Case 1 would have been screened as per the G-ROP screening criteria, due to 240 g weight loss between days 10–19. Case 2 had adequate weight gain until day 29. However, over days 30–35, net weight gain was just 16 g, indeed losing 6 g over days 32–35. We do not have weight data beyond this period, but we can assume that this baby would not have subsequently gained enough to satisfy G-ROP weight gain criteria. Case 3 lost 820 g in the first week of life, following drainage of a large renal cyst. On the basis of subsequent weight gain alone, this baby would not have been eligible for screening as per G-ROP. However, given that hydrocephalus is included as a discrete and absolute criterion for screening in G-ROP, we consider that the renal cyst (analogous to hydrocephalus as a non-physiological fluid reservoir that might confound weight gain interpretations) reasonably warranted screening as per G-ROP. Case 4, with weight loss of 470 g between days 29–37, would also have been screened as per G-ROP. Case 5 gained just 100 g between days 30–36, which approximated G-ROP screening criteria (i.e., weight gain of <170 g over days 30–39). We cannot extrapolate the weight gain for this child over days 37–39 with certainty, but it is likely that this infant would have hit the G-ROP screening criteria. Weight gain data for case 6 is available only for the first 34 days. In the first 28 days, the weight gain was well above G-ROP criteria. However, across days 29–34, weight gain was just 100 g. It is notable that whilst at least five of our reported babies likely fulfilled the weight gain criteria for screening as per G-ROP, none would have fulfilled the criteria for screening according to EL-ROP, an algorithm incorporating maternal ethnicity derived from a retrospective observational data set of multi-ethnic babies from the UK [13].

We report six retrospective cases of sight-threatening, treated ROP that would have fallen outside the updated criteria for ROP screening in the UK. Each infant had an unstable postnatal course;

**Table 1.** Clinical overview for each case.

Case (Year)	GA (weeks)	BW (g)	ROP classification at time of treatment	
			Right	Left
1 (2017)	31 + 4	2000	Stage 3	Stage 3
			Zone 2	Zone 2
			No plus	Plus
2 (2020)	31 + 2	1774	Stage 3	Stage 3
			Zone 3	Zone 3
			Plus	Plus
3 (2021)	31 + 1	2771	AP-ROP	AP-ROP
4 (2021)	31 + 5	1659	Stage 3	Stage 2
			Zone 2	Zone 2
			Plus	Plus
5 (2022)	31 + 4	1680	Stage 3	Stage 3
			Zone 2	Zone 2
			No plus	No plus
6 (2023)	31 + 3	1560	Stage 3	Stage 3
			Zone 3	Zone 3
			Plus	Plus

GA gestational age, BW birth weight, ROP retinopathy of prematurity, AP-ROP aggressive posterior retinopathy of prematurity.

**Table 2.** Risk factor profile for each case.

Risk factors	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Maternal prenatal steroid	✓	✓	✓			✓
Twin-to-twin transfusion	✓					
Blood transfusion	✓	✓		✓		
Respiratory distress syndrome	✓	✓	✓	✓	✓	✓
Surfactant	✓	✓		✓	✓	
Bronchopulmonary dysplasia	✓					
Suspected sepsis	✓		✓	✓		✓
Confirmed sepsis		✓				
Anaemia				✓		
Thrombocytopenia				✓		
Polycythaemia neonatorum			✓			
Intra-ventricular haemorrhage		✓	✓			
Multiple gestations	✓				✓	✓
Congenital hydrocephalus		✓				

**Table 3.** Postnatal weight gain for each case, stratified as per G-ROP criteria.

Postnatal age (interval, days) <sup>a</sup>	10–19	20–29	30–39
Weight gain (g)	<120	<180	<170
Case 1	–240	+365	+280
Case 2	+210	+190	+16
Case 3	+150	+200	+300
Case 4	No data	+307	–470
Case 5	+150	+260	+100
Case 6	+320	+240	+100

<sup>a</sup>Where available data was not recorded according to the precise corresponding time interval of G-ROP, the closest range was used. Box shading indicates fulfilment of G-ROP screening criteria.

all had poor weight gain and 3 had multiple additional risk factors for ROP. If examination had not been carried out and timely treatment administered, these infants might have gone on to lose vision. We believe that the current iteration of the UK screening guidelines presents an unacceptable risk; it must be recalled and reconsidered. If screening by reduced GA criteria is to be maintained safely, incorporation of other known risk factors for ROP such as weight gain (and non-physiological confounders of this) must be incorporated. This, alongside careful considerations about the practicalities of implementing less binary criteria in a pressurised clinical environment. Failure to do so risks inexcusably forfeiting the opportunity to diagnose and treat a preventable cause of life-long blindness.

## SUMMARY

What was known before

- The significant burden and potential morbidity of retinopathy of prematurity (ROP) screening was recognised, and new UK screening guidance was released in March 2022
- Birth weight criteria did not alter, but the gestational age cut-off was reduced from <32 weeks to <31 weeks
- No additional screening parameters were incorporated

What this study adds

- Six cases that did not fulfil the new screening criteria, but went on to develop severe ROP requiring treatment are reported
- These cases had several systemic risk factors for the development of ROP
- We propose the need to recall and revise the latest guidance, to incorporate additional systemic risk factors such as postnatal weight gain

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## AUTHOR CONTRIBUTIONS

Concept of work: RJH, SA. Acquisition of data: all authors. Drafting of manuscript: RJH, SA. Reviewing manuscript critically: all authors. Final approval of manuscript: all authors. Accountability for all aspects of the work: RJH, SA.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

**Correspondence** and requests for materials should be addressed to Roxane J. Hillier.

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