Visual impairment due to retinopathy of prematurity (ROP) in New Zealand: a 22-year review

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ABSTRACT

Aim To evaluate retinopathy of prematurity (ROP)related visual impairment in New Zealand children. **Methods** 22-year retrospective review of medical records of children with moderate to severe visual impairment registered with the Blind and Low Vision Education Network New Zealand. The cohort was divided into two periods (1991–2004; 2005–2012) for analysis.

Results 232 children with ROP were treated in the study period (109 in period 1, 123 in period 2). 36 children, 63.9% of whom were of male sex, were identified with subsequent significant visual impairment (27 in period 1, 9 in period 2). The incidence of new cases of visual impairment from ROP declined from 271.6 infants/100 000 live very preterm births per annum (period 1) to 146.1 per annum (period 2). Mean gestational age and mean birth weight were comparable between the two study periods. 75% of children with visual impairment from ROP received treatment for their condition (period 1, 74.1%; period 2, 77.8%) and modalities used changed significantly over time. The modal visual outcome overall was Snellen visual acuity <6/18-6/60 (55.6%) (period 1, 51.9%; period 2, 66.7%). The proportion of children with no light perception bilaterally decreased over time (period 1, 3.7%; period 2, 0%).

Conclusions There has been a reduction in the incidence of infants with significant visual impairment from ROP over time in New Zealand, likely due to progress in clinical management of ROP. Our study suggests the current ROP screening criteria of <31 weeks' gestation or <1250 g are of sufficient breadth.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina in preterm infants that may lead to severe visual impairment. Following recent basic science studies, the pathogenesis of ROP is now much better understood, but the major risk factors remain increasing prematurity, lower birth weight and poorly monitored oxygen levels.^{1 2}

Progressive improvements in neonatal intensive care over the past two decades have led to increased survival of very preterm (VP, \leq 31 weeks' gestation) infants.³ ⁴ Hence, while most data suggest the incidence of ROP in VP infants in developed countries has either remained fairly constant² or declined somewhat,⁵ the absolute number of ROP cases is likely to have increased. At the same time, developing neonatal care in middle-income countries has been accompanied by a rise in the number of cases of ROP, including infants with greater birth weight and higher gestational age than are routinely affected in high-income countries.^{6–8} Over 30 000 infants world-wide are visually impaired from ROP annually, and it is estimated 65% of these infants come from middle-income countries.⁶

While most ROP regresses, the disease can progress to cause severe visual impairment or blindness. Recent estimates suggest around 10% of childhood blindness in developed countries is caused by cicatricial ROP.9 Case detection by fundus examination at an appropriate time, generally 4-6 weeks postnatal or between 31 and 33 weeks' gestation, allows identification of eyes with severe ROP that will benefit from treatment. The Cryotherapy for Retinopathy of Prematurity trial,¹⁰ which randomised eyes to treatment or observation when the stage of the disease ('threshold disease') posed a roughly 50% risk of adverse outcome, was a major advance in preventing loss of vision from ROP. In 1986, the year prior to cryotherapy treatment becoming available, a prospective audit of all very low-birthweight infants (VLBW, birth weight <1250 g) admitted for neonatal intensive care in New Zealand identified six infants who became bilaterally blind from ROP.11

Treatment of severe ROP is now usually undertaken by laser photocoagulation and a large randomised trial (Early Treatment of Retinopathy of Prematurity (ETROP)) has shown improved structural and functional outcomes from treating severe ROP at an earlier stage of the acute disease (termed 'type 1 ROP').¹² Most ophthalmologists treating ROP in New Zealand adopted ETROP criteria by 2005. In the last few years, intravitreal bevacizumab has also become an option, although somewhat controversial, for the treatment of severe zone 1 ROP.^{13 14}

New Zealand has around 60 000 births annually with most VP and VLBW infants being cared for in one of six regional ('level III') neonatal intensive care units (NICUs). Infants not requiring tertiarylevel care are managed in 1 of 16 level II units. Since 1998, all level III and II NICUs have contributed data to the Australian and New Zealand Neonatal Network (ANZNN) ongoing audit of VP and VLBW infants.

Using data from the ANZNN and Statistics New Zealand, the annual incidence of VP births has increased slightly from 1991 to 2012, and the incidence of severe ROP has changed relatively little.^{15–17} However, there is only sparse information on the incidence of ROP-related visual impairment in New Zealand, especially as its management has changed over time. Hence, the first aim of this study was to assess the incidence of

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To cite: Tan Z, Chong CF, Darlow B, *et al. Br J Ophthalmol* Published Online First: [*please include* Day Month Year] doi:10.1136/bjophthalmol-2014-305913 significant visual impairment attributable to ROP in New Zealand over the past 22 years.

The results of the 1986 prospective audit of ROP led to a recommendation that all infants of <31 weeks' gestation or <1250 g birth weight be screened for ROP.¹⁸ This national recommendation has not been formally reassessed since then, and it is clearly timely now to review these recommendations. The second aim of this study was therefore to seek information to inform this review.

METHODS

Patients and procedures

Data from this study were collected from the registry of students at the Blind and Low Vision Education Network New Zealand (BLENNZ), a national organisation that offers multidisciplinary support to all blind and visually impaired children in New Zealand.¹⁹ All children and young people aged 0-21 with corrected visual acuity (VA) < 6/18 in the better seeing eye and who access government funding and support are registered with BLENNZ. All students enrolled at BLENNZ had been previously examined by their primary ophthalmologists, and the majority had also been examined by the BLENNZ visiting ophthalmologist (SD). The BLENNZ registry is live and once registered students reach 21 years of age, they are deregistered and their information transferred to the New Zealand Blind Foundation, with the consent of the students or their next of kin. Causes of visual impairment were coded according to the WHO/PBL Eye Examination Record for Children with Blindness and Low Vision form.²⁰

A retrospective review was conducted and the medical records of all 1142 students at BLENNZ were reviewed. Only children who were born in New Zealand between 1991 and 2012 and whose primary cause of visual impairment was ROP (determined after reviewing medical notes or examining the child in case of any ambiguity) were included in our study cohort. The diagnosis of ROP-related visual impairment was made by at least two independent ophthalmologists on separate occasions. 1991 was set as the start date as the live BLENNZ registry enrolled children between 0 and 21 years of age, and the study duration of 1991–2012 coincided with the BLENNZ database inclusion age criterion. Hence, all children born within the study duration were still captured within the live registry.

Medical and ophthalmic histories were reviewed, with ROP treatment status, gestational age and birth weight noted specifically. Age, gender and ethnicity demographics were recorded. Collected data were verified with original medical and ROP screening records located at their respective hospital sites.

The best-corrected VA at the last available assessment provided by the BLENNZ visiting ophthalmologist (SD) was recorded. VA was measured using the Snellen chart where possible and failing that a variety of age-appropriate visual assessments were conducted (optokinetic drum, 100s and 1000s, forced preferential testing, picture matching).

The International Classification of Diseases-10 definitions of visual impairment were followed.²¹ Mild or no visual impairment was considered to be $\geq 6/18$, moderate visual impairment < 6/18-6/60 and severe visual impairment < 6/60-3/60. Blindness was defined as best-corrected VA in the better eye of < 3/60. In this study, the term significant visual impairment was used to encompass moderate visual impairment to blindness. Data on the number of children treated for ROP were obtained from ANZNN,¹⁵ and data on the New Zealand birth rate and ethnic groups were obtained from Statistics New Zealand.¹⁷

Data collected for this 22-year retrospective period (1991–2012) were divided into two study periods for comparison: children born in period 1 (1991–2004) and children born in period 2 (2005–2012). ROP screening and treatment practice changed significantly in 2005 following the outcomes of the ETROP trial,^{12 22} and division into these two study periods was conducted in order to evaluate the impact of these changes on the outcomes of ROP care in New Zealand.

Statistical analysis

Clinical data from the two study periods were analysed using independent sample t tests and Fisher's exact test for gender. Differences with a p value of <0.05 were considered significant.

Changes in the incidence of visual impairment resulting from ROP are reported observationally. This is due to the limited size and statistical power of this study cohort, excluding the use of further statistical analysis via logistic regression.

Statistical support was provided by the Department of Statistics, University of Auckland. Statistical analysis was conducted using the commercial software package Graphpad Prism (Graphpad Prism Software, San Diego, California, USA).

RESULTS

During the study period, 232 children with ROP were treated, with 109 cases in period 1 (1991–2004) and 123 cases in period 2 (2015–2012). Thirty-six infants (63.9% of male sex) with ROP-related significant visual impairment were identified. At the end of 2012 and the commencement of this study, the average age of infants in this study cohort was 12.2 years and the median age 13 years. The range of ages was from 17 months to 21 years.

The incidence of infants with ROP-related significant visual impairment is presented in figure 1. The percentage of infants treated for ROP who developed significant visual impairment declined from 24.8 in period 1 (1991–2004) to 7.3 in period 2 (2005–2012) (table 1). A downward trend is also observed in the absolute incidence of ROP-related visual impairment. Also, 1.9 infants per annum developed visual impairment from ROP in period 1, which declined to a mean of 1.1 infants per annum in period 2. At the same time, the number of ROP cases treated increased from 7.8 per annum in period 1 to 15.3 per annum in period 2. Normalised for changes in the number of VP infants born every year in New Zealand, the incidence of infants with visual impairment caused by ROP declined from 271.6 infants/ 100 000 live VP live births per annum in period 1 to 146.1 per annum in period 2.

Neonatal data are presented in table 2. The mean gestational age of infants overall was 25.4 ± 2.0 weeks (period 1, 25.4 ± 2.0 weeks; period 2, 25.6 ± 1.9 weeks) and mean birth weight of infants overall was 787.0 ± 222.5 g (period 1, 778.9 ± 220.9 g; period 2, 835.8 ± 225.6 g). There was no statistically significant difference in the birth weight or gestational age between the cohorts in the two periods. Similarly, the distribution of gestational ages and birth weights was comparable across the two study periods (table 2).

The ethnicities of infants in this review are presented in table 3. Most affected children were of European descent (50.0%). Children of Māori (25.0%), Pacific peoples (8.3%), Asian (8.3%), unspecified ethnicity (5.6%) and Middle Eastern/Latin American/ African (2.8%) descent made up the remainder. This ethnic breakdown is consistent with the general ethnic makeup of young people in New Zealand aged 0–20.

Treatment status and modalities are presented in table 4. Seventy-five per cent of infants overall received treatment for their ROP (period 1, 74.1%; period 2, 77.8). Some infants may

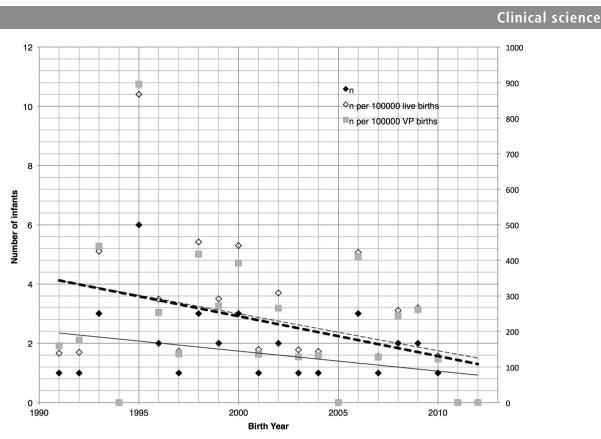


Figure 1 Incidence of visual impairment caused by retinopathy of prematurity in New Zealand. Solid line: n. Light dashed line: n per 100 000 live births. Heavy dashed line: n per 100 000 very preterm births. VP, very preterm.

have received multiple modalities of treatment, and the modalities used changed considerably over time. In period 1, retinal cryotherapy (40.0%), laser photocoagulation (75.0%) and retinal detachment surgery (30.0%) were used. In period 2, treatment comprised laser photocoagulation (100.0%) and intravitreal bevacizumab (14.3%).

Visual outcomes of the subjects enrolled in this study, as arranged per their better seeing eye, are presented in table 5. Also, 18.5% of infants born in period 1 had mild impairment visually (VA 6/12–6/18) at the time of this review, although their visual acuities were recorded as $\leq 6/18$ at their initial registration with BLENNZ. Infants who had an eye with mild visual

Period	Period 1 1991– 2004	Period 2 2005– 2012	Overall 1991– 2012
Number of infants	27	9	36
Number of infants treated for ROP	109	123	232
Average number of infants treated for ROP per annum	7.8	15.4	10.5
Percentage of treated infants with visual impairment	24.8	7.3	15.5
Number of total live births×100 000	8.0	4.9	13.0
Number of visually impaired infants/ 100 000 live births	3.4	1.8	2.8
Mean number of live VP births per annum	710.1	769.9	731.9
Number of visually impaired infants/ 100 000 live VP births	271.6	146.1	223.6

impairment (6/12–6/18) invariably all had a second eye with moderate or worse visual impairment (<6/18). Eyes with mild visual impairments resulted from the development of retinal folds following cryotherapy treatment. There were no infants with mild visual impairment in period 2. The proportion of infants with moderate impairment (<6/18–6/60) increased between period 1 and period 2 (51.9–66.7%). The proportion of infants with no light perception bilaterally decreased from period 1 to 2 (3.7–0%).

Concomitant disabilities are presented in table 6. Developmental delay was identified as the most common comorbidity in 50% of infants.

DISCUSSION

With progressive advances in ROP management, the incidence of adverse outcomes and visual impairment from ROP in developed countries worldwide is declining.⁵ ⁹ ^{23–25} Our findings support this trend in New Zealand, with a decrease in the incidence of infants with visual impairment caused by ROP from 1991 to 2012 (figure 1 and table 1).

These changes are in the context of a slight increase in the annual incidence of VP births over the same time.¹⁵ ¹⁷ Gestational age and birthweight risk factors that predispose infants to ROP remained consistent throughout the course of our study periods (figure 2 and table 2). As such, factors related to improvements in ROP screening and treatment are likely to have contributed to the observed reduction in ROP-associated visual impairment.

Over the past 10 years, ROP screening and treatment in most level III New Zealand centres have been carried out by fellowship trained paediatric or retinal specialists experienced in ROP diagnosis. Some centres in New Zealand have also introduced routine use of the Retcam wide-field retinal imaging system for screening,

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Table 2	Neonatal data from New Zealand infants with visual impairment caused by retinopathy of prematurity in two consecutive survey
periods	

Period	Period 1 1991–2004	Period 2 2005–2012	p Value	Overall 1991–2012
Infants (n)	29	7		36
Men (%)	59.3%	77.8%	ns (p=0.438)	63.9%
Mean gestational age (weeks)	25.4±2.0	25.6±1.9	ns (p=0.851)	25.4±2.0
Gestational age distribution (% (n)), we	eks			
22	3.7% (1)	0% (0)		2.8% (1)
23	11.1% (3)	11.1% (1)		11.1% (4)
24	22.2% (6)	33.3% (3)		25.0% (9)
25	22.2% (6)	11.1% (1)		19.4% (7)
26	14.8% (4)	11.1% (1)		13.9% (5)
27	7.4% (2)	0% (0)		5.6% (2)
28	14.8% (4)	33.3% (3)		19.4% (7)
29	0% (0)	0% (0)		0% (0)
30	0% (0)	0% (0)		0% (0)
31	3.7% (1)	0% (0)		2.8% (1)
Mean birth weight (g)	778.9±220.9	835.8±225.6	ns (p=0.542)	787.0±222.5
Birth weight distribution (% (n)), g				
<500	0% (0)	11.1% (1)		2.8% (1)
501–750	51.9% (14)	33.3% (3)		47.2% (17)
751–1000	33.3% (9)	33.3% (3)		33.3% (12)
1001–1250	7.4% (2)	22.2% (2)		11.1% (4)
1251–1500	7.4% (2)	0% (0)		5.6% (2)

which may have resulted in treatment-warranted ROP being detected more timely in centres where ROP screening was known to be previously inadequate.^{26 27} As well, the implementation of guidelines following the ETROP trial (tables 1, 4 and 5)¹² in 2005 (period 2) has resulted in earlier treatment and treatment of a larger number of infants with less advanced ROP, and this may have also contributed to improved visual outcomes.

In our first study period, 18.5% of infants (table 5) with ROP-associated visual impairment had VA between 6/12 and 6/18 due to retinal folds. This has not been observed in our second period. Improvements in treatment technique and modalities may be partially responsible for this.

Thus, overall, it seems reasonable to suggest that improvements in the clinical management of ROP may have contributed

Table 3	Ethnicity of New Zealand infants with visual impairment
caused by	retinopathy of prematurity in two consecutive study
periods	

Period	Proportion of New Zealand population aged 0–20 (%)	Period 1 1991–2004	Period 2 2005–2012	Overall 1991–2012
Infants (n)		27	9	36
European	68.8	48.2% (13)	55.6% (5)	50.0% (18)
Māori	22.5	33.3% (9)	0% (0)	25.0% (9)
Pacific Peoples	11.8	3.7% (1)	22.2% (2)	8.3% (3)
Asian	11.6	7.4% (2)	11.1% (1)	8.3% (3)
Middle Eastern/ Latin American/ African (MELAA)	1.4	0% (0)	11.1% (1)	2.8% (1)
Other	11.1	0% (0)	0% (0)	0% (0)
Unspecified	N/A	7.4% (2)	0% (0)	5.6% (2)

to the reduction in the rate of visual impairment and adverse outcomes developing from ROP.

It has to be noted that 22.2% of infants with severe ROP across both study periods were not treated as their ROP were too advanced at the time of diagnosis for available treatments to be effective. The majority of these cases were either due to delays in the diagnosis of severe ROP or timely transfer to a level III NICU for treatment. Two cases were due to lack of proper communication between transferring and receiving units, and this resulted in missed ROP diagnosis.

The second aim of this study was to evaluate the efficacy of the inclusion criteria used in New Zealand for ROP screening,

Table 4 Treatment status and modality in New Zealand infants
with visual impairment caused by retinopathy of prematurity in two
consecutive study periods

Period	Period 1 1991–2004	Period 2 2005–2012	Overall 1991–2012	
Infants (n)	27	9	36	
Treatment status (some patients may have received more than one treatment modality)				
Yes—any modality*	74.1% (20)	77.8% (7)	75.0% (27)	
Retinal cryotherapy	29.6/40.0%** (8)	0/0% (0)	22.2/29.6% (8)	
Laser photocoagulation	55.6/75.0% (15)	77.8/100.0% (7)	61.1/81.5% (22)	
Retinal detachment surgery	22.2/30.0% (6)	0/0% (0)	16.7/22.2% (6)	
Intravitreal bevacizumab	0/0% (0)	11.1/14.3% (1)	2.8/3.7% (1)	
No treatment	22.2% (6)	22.2% (2)	22.2% (8)	
Unspecified	3.7% (1)	0% (0)	2.8% (1)	

*Any modality includes cryotherapy, laser photocoagulation, retinal detachment surgery or intravitreal bevacizumab. **Percentage of infants compared to the number of infants overall/percentage of

infants compared to only the number of infants treated.

Table 5	VA of New Zealand infants with visual impairment
caused by	retinopathy of prematurity in two consecutive study
periods	

Period	Period 1 1991–2004	Period 2 2005–2012	Overall 1991–2012
Infants (n)	27	9	36
Mild visual impairment VA 6/12–6/18	18.5% (5)	0% (0)	13.9% (5)
Moderate visual impairment VA <6/18–6/60	51.9% (14)	66.7% (6)	55.6% (18)
Severe visual impairment VA <6/60–3/60	3.7% (1)	11.1% (1)	5.7% (2)
<3/60—LP	14.8% (4)	22.2% (2)	16.7% (6)
NLP	3.7% (1)	0% (1)	2.8% (1)
Hand movements	7.4% (2)	0% (0)	5.6% (2)

LP, light perception; NLP, no light perception; VA, visual acuity.

which are <31 weeks' gestation or <1250 g birth weight.¹⁸ However, three level III units have set their screening criteria at <30 weeks' gestation or <1250 g based on their clinical audit results.²⁸ These recommendations also suggest ROP screening examination for selected infants \geq 1250 g and \geq 30 weeks with an unstable clinical course who are believed to be at high risk by their attending neonatologist. These inclusion criteria are more restrictive than the birth weight and gestational age values recommended in guidelines published by the American Academy of Pediatrics about which there remains substantial debate.²² Under the first category of the revised New Zealand criteria (<1250 g birth weight or <30 weeks' gestation), all but 1 of the 36 infants identified in this present review would have been included for screening, and if appropriate, subsequent treatment (table 2). This infant, born in 1995 at 31 weeks' gestation and 1260 g, and thus just outside of the published criteria for screening, would have likely been included for screening

Table 6Concomitant disabilities in New Zealand infants with
visual impairment caused by retinopathy of prematurity in two
consecutive study periods

Period	Period 1 1991–2000	Period 2 2001–2012	Overall 1991–2012
Infants (n)	27	9	36
Behavioural abnormalities	22.2% (6)	0% (0)	16.7% (6)
Cerebral palsy	22.2% (6)	22.2% (2)	22.2% (8)
Developmental delay	55.6% (15)	33.3% (3)	50.0% (18)
Epilepsy	11.1% (3)	11.1% (1)	11.1% (4)
Hearing deficit	18.5% (5)	0% (0)	13.9% (5)

under the provision of the second criteria category of having an unstable clinical course. This finding thus provides evidence to the assertion that inclusion criteria used here in New Zealand for ROP screening are of sufficient efficacy and breadth.²⁸

The visual outcomes and concomitant disabilities of infants identified in this review were similar to those previously reported overseas.²⁵

We acknowledge that this study may have underreported the true incidence of visual impairment caused by ROP BLENNZ registers all visually impaired children and young people aged between 0 and 21 who access government health funding, social and educational support in New Zealand, but this is limited to those with best-corrected VA in the better eye of $\leq 6/18$. While BLENNZ captures the vast majority of children with visual impairment, inevitably a small minority of children may not be registered. This may particularly affect those with mild visual impairment (BLENNZ registration criterion is corrected VA of $\leq 6/18$). With this caveat, however, we do expect that our cohort has captured the vast majority of young people with visual impairment due to ROP in New Zealand, particularly as there are no private health providers for neonatal services in this country.

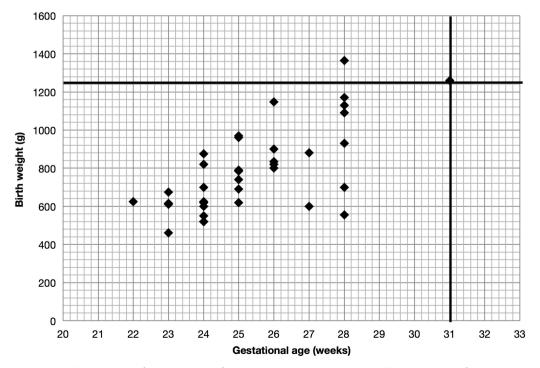


Figure 2 Gestational age and birth weight of New Zealand infants with visual impairment caused by retinopathy of prematurity. The reference lines indicate screening criteria of <31 weeks' gestation or <1250 g used currently in New Zealand.

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An additional limitation to this study is its retrospective nature. Due to the small size of the cohort and subsequent limited statistical power, findings reported here are observational.

This study has shown that there has been a reduction in the number of infants with visual impairment from ROP over time in New Zealand. We suggest that this improved outcome may be partially due to the result of progress made in the clinical management and treatment of ROP in New Zealand, including the introduction of new screening practices such as the use of Retcam wide-field retinal imaging in larger centres in New Zealand.²⁶ ²⁷ This study also suggests that the current ROP screening criteria of <31 weeks' gestation or <1250 g are adequate. This reviews the recommendations made in 1986¹¹ and supports the assertion that inclusion criteria used now in New Zealand for ROP screening are of sufficient efficacy and breadth.

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Contributors All articles are given credit for (1) substantial contributions to conception and design, acquisition of data or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

Competing interests None.

Ethics approval This study was approved by the Northern Regional Ethics Committee for health research in New Zealand and adhered to the tenets of the declaration of Helsinki.

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Data sharing statement All data collected in this study have been included for publication.

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