Antibiotics for early-onset neonatal infection

Evidence Update June 2014

A summary of selected new evidence relevant to NICE clinical guideline 149 ‘Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection’ (2012)

Evidence Update 62
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Introduction

Evidence Updates are intended to increase awareness of new evidence – they do not replace current NICE guidance and do not provide formal practice recommendations.

Evidence Updates reduce the need for individuals, managers and commissioners to search for new evidence. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline.

This Evidence Update provides a summary of selected new evidence published since the literature search was last conducted for the following NICE guidance:

1. **Antibiotics for early-onset neonatal infection.** NICE clinical guideline 149 (2012)

A search was conducted for new evidence from 1 September 2011 to 15 January 2014. A total of 7838 pieces of evidence were initially identified. After removal of duplicates, a series of automated and manual sifts were conducted to produce a list of the most relevant references. The remaining 28 references underwent a rapid critical appraisal process and then were reviewed by an Evidence Update Advisory Group, which advised on the final list of 5 items selected for the Evidence Update. See Appendix A for details of the evidence search and selection process.

Evidence selected for inclusion in this Evidence Update may highlight a potential impact on guidance: that is, a high-quality study, systematic review or meta-analysis with results that suggest a change in practice. Evidence that has no impact on guidance may be a key read, or may substantially strengthen the evidence base underpinning a recommendation in the NICE guidance.

The Evidence Update gives a preliminary assessment of changes in the evidence base and a final decision on whether the guidance should be updated will be made by NICE according to its published processes and methods.

This Evidence Update was developed to help inform the review proposal on whether or not to update NICE clinical guideline 149 (**NICE CG149**). The process of updating NICE guidance is separate from both the process of an Evidence Update and the review proposal.

See the NICE clinical guideline development methods for further information about updating clinical guidelines.

Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other NICE guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

1. **Intrapartum care.** NICE clinical guideline 55 (2007) (currently **being updated**)

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1 NICE-accredited guidance
NICE Pathways

NICE Pathways bring together all related NICE guidance and associated in a set of interactive topic-based diagrams. The following NICE Pathway covers advice and recommendations related to this Evidence Update:

- Antibiotics for early-onset neonatal infection. NICE Pathway

Feedback

If you would like to comment on this Evidence Update, please email contactus@evidence.nhs.uk
### Key points

The following table summarises the key points for this Evidence Update and indicates whether the new evidence may have a potential impact on NICE CG149. Please see the full commentaries for details of the evidence informing these key points.

The section headings used in the table below are taken from NICE CG149.

Evidence Updates do not replace current NICE guidance and do not provide formal practice recommendations.

<table>
<thead>
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<th>Potential impact on guidance</th>
<th>Key point</th>
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<th>Risk factors for infection and clinical indicators of possible infection</th>
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<tr>
<td><strong>Epidural anaesthesia</strong></td>
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<td>• Epidural anaesthesia may be a risk factor for early-onset neonatal fever, irrespective of intrapartum fever, but is not associated with a higher incidence of neonatal infection.</td>
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<th>Investigations before starting antibiotics in the baby</th>
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<td><strong>Full blood count</strong></td>
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<td><strong>Serum procalcitonin concentration</strong></td>
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<td><strong>Gentamicin dosing</strong></td>
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<th>Duration of antibiotic treatment</th>
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<td><strong>Serial C-reactive protein measurement</strong></td>
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<td>• Antibiotic treatment could be safely stopped at 48 hours in culture-negative infants of very low birth weight who have C-reactive protein concentrations of less than 10 mg/litre at presentation and at 48 hours.</td>
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1 Commentary on new evidence

These commentaries focus on the ‘key references’ identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update, which are shown in bold text. Section headings are taken from NICE CG149.

1.1 Information and support

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.2 Risk factors for infection and clinical indicators of possible infection

Epidural anaesthesia

NICE CG149 specifies 8 risk factors for early-onset neonatal infection and 23 clinical indicators of possible infection. ‘Red flag’ risk factors and clinical indicators are those that should prompt a high level of concern regarding early-onset neonatal infection. After the birth in babies with any ‘red flag’ risk factors or clinical indicators, or with two or more ‘non-red flag’ risk factors or clinical indicators, investigations should be performed and the infant started on antibiotic treatment.

The full version of NICE CG149 refers to the full version of NICE clinical guideline 55 ‘Intrapartum care’ (NICE CG55, currently being updated). NICE CG55 considers maternal fever associated with epidural anaesthesia a potential risk factor for neonatal infection, but does not make any recommendations in this area. NICE CG149 lists intrapartum fever higher than 38°C and infant temperature lower than 36°C or higher than 38°C unexplained by environmental factors as risk factors and clinical indicators of early-onset neonatal infection.

Agakidis et al. (2011) conducted a retrospective cohort study of data from a single centre in Scotland to determine whether epidural anaesthesia was a risk factor for neonatal fever after controlling for maternal intrapartum fever. The analysis included all term singleton neonates born consecutively over a 10 month period to mothers who received epidural anaesthesia during labour (n=480). These infants were compared with term singleton neonates born during the same period to mothers who did not receive epidural anaesthesia (n=480). Neonatal temperature had been measured in the axilla at 1 hour and 2 hours after birth, then every 2 hours for 12 hours and every 4 hours thereafter until discharge. Fever was defined as a temperature of 38°C or more in the mothers and more than 37.5°C in the infants.

Mothers and infants in the epidural anaesthesia group were significantly more likely to have had fever than were those in the no epidural group (odds ratio [OR] for intrapartum fever=15.08, 95% confidence interval [CI] 5.42 to 42.00, p<0.0001 and OR for neonatal fever=5.11, 95% 2.88 to 9.10, p<0.0001). Neonatal fever remained more common in the epidural anaesthesia group when only infants whose mothers did not have fever were analysed (n=895; OR=4.09, 95% CI 2.26 to 7.39, p<0.0001). Although infants whose mothers had undergone epidural anaesthesia were more likely to undergo sepsis screen and receive antibiotics (p<0.0001 for both), no positive blood cultures were reported in any neonates assessed for sepsis. Epidural anaesthesia was an independent risk factor for neonatal fever, both in all mother–infant pairs (adjusted OR=3.46, 95% CI 1.88 to 6.35, p<0.0001) and in pairs where the mother did not have fever (adjusted OR=3.32, 95% CI 1.80 to 6.15, p<0.0001).

This study was limited by its retrospective design and that it used data from a single centre. In addition, only 19 (4%) infants in the epidural anaesthesia group had a temperature of 38°C.
or more, the level at which NICE CG149 defines fever, and only 68 (14%) had a temperature of more than 37.5°C. The number of infants with fever whose mothers did not have epidural anaesthesia was also low (n=15, 3%). These small numbers of infants with fever may have limited the power of some analyses.

The evidence suggests that epidural anaesthesia may be a risk factor for early-onset neonatal fever, irrespective of intrapartum fever, but is not associated with a higher incidence of neonatal infection. In infants with fever whose mothers had epidural anaesthesia, and in the presence of no other risk factors or clinical features of neonatal infection, observation is appropriate instead of investigations and treatment for sepsis. This evidence is unlikely to have an impact on NICE CG149 given the small numbers of infants with fever in the study.

**Key reference**

### 1.3 Intrapartum antibiotics

No new key evidence for this section was selected for inclusion in this Evidence Update.

### 1.4 Avoiding routine use of antibiotics in the baby

No new key evidence for this section was selected for inclusion in this Evidence Update.

### 1.5 Investigations before starting antibiotics in the baby

**Full blood count**

During the development of NICE CG149, peripheral white blood cell count, absolute neutrophil count and immature to total neutrophil ratio (I:T ratio) were considered for ruling in early-onset neonatal infection in asymptomatic babies with at least one risk factor. However, the health economic analysis conducted for the guideline did not provide robust evidence of the cost effectiveness of full blood count in asymptomatic babies, so NICE CG149 does not recommend its use. In addition, the diagnostic test accuracy of full blood count was not sufficiently strong to recommend its use at presentation in babies about to start antibiotic treatment.

Hornik et al. (2012) conducted a retrospective cohort study to evaluate the accuracy of full blood count in diagnosing early-onset infection in neonates. Demographic, culture (blood, urine or cerebrospinal fluid), and full blood count data were obtained for neonates admitted to 293 US neonatal intensive care units over a 13 year period. Early-onset infection was defined as a positive culture during the first 3 days of life. A total of 166,092 neonates with 171,376 cultures were identified; 2177 (1.3%) positive cultures in 2164 (1.3%) neonates were recorded.

Low white blood cell count (<8800/mm³) was associated with an increased odds of culture-proven early-onset infection (OR=1.53, 95% CI 1.13 to 2.06), but high white blood cell count did not increase the odds of infection. An absolute neutrophil count of less than 4134/mm³, a platelet count of less than 147,000/mm³, and an I:T ratio of more than 0.24 were also all associated with early-onset infection (data reported graphically). The sensitivity of the blood count indices for early-onset infection was low, with the highest sensitivity observed for an I:T ratio of more than 0.24 (49.2%). Specificity was generally higher, with the lowest specificity for an absolute neutrophil count of less than 4134/mm³ (74.3%). The positive likelihood ratios ranged from 1.5 for a platelet count of less than 147,000/mm³, to 2.5 for an I:T ratio of more than 0.24. The negative likelihood ratios ranged from 0.6 for an I:T ratio of more than 0.24, to 1 for a platelet count of less than 147,000/mm³.
Limitations of the evidence include that it was a retrospective analysis and that the database lacked information on infants’ previous exposure to antibiotics before culture samples were taken. No information was available on whether the infants were symptomatic at the time the culture was taken. Little data was available on maternal risk factors unrelated to infection that might affect neonatal blood counts (for example, maternal hypertension and preeclampsia, which may cause neonatal neutropenia and thrombocytopenia).

The evidence suggests that full blood count indices may not be sufficiently sensitive to rule out early-onset infection in neonates. This evidence is unlikely to have an impact on NICE CG149, which does not recommend full blood count for the diagnosis of early-onset neonatal infection.

Key reference

Serum procalcitonin concentration
The full version of NICE CG149 states that at the time of guideline development, measurement of serum procalcitonin concentration was insufficiently useful to accurately rule in or rule out early-onset neonatal infection in babies about to start antibiotic treatment. As such, NICE CG149 does not does not include any recommendations on using this marker to diagnose neonatal infection.

A systematic review and meta-analysis by Vouloumanou et al. (2011) assessed the value of serum procalcitonin testing for the diagnosis of early-onset neonatal infection. The analysis included studies that compared serum procalcitonin concentration in neonates with microbiologically or clinically confirmed sepsis with levels in neonates in whom sepsis had been excluded. To be included, studies needed to have measured serum procalcitonin concentration at presentation in babies with suspected sepsis before the use of antibiotics.

In a pooled analysis of the 16 cohort and case–control studies identified (n=1959), the sensitivity of serum procalcitonin concentration for the diagnosis of neonatal sepsis was 81% (95% CI 74 to 87%) and the specificity was 79% (95% CI 69 to 87%). The pooled positive and negative likelihood ratios were 3.9 (95% CI 2.5 to 6.0) and 0.24 (95% CI 0.17 to 0.34), respectively. A subanalysis of 6 studies of early-onset sepsis (sepsis diagnosed in the first 72 hours of life, n=780) found a lower pooled sensitivity (76%, 95% CI 68 to 82%) and specificity (76%, 95% CI 60 to 87%). The pooled positive and negative likelihood ratios were 3.2 (95% CI 1.8 to 5.7) and 0.32 (95% CI 0.23 to 0.43), respectively. A range of cut off values for procalcitonin were identified – from ≥0.5 ng/ml to >5.75 ng/ml – but the effect of a diagnostic threshold was not found to be important.

Limitations of the evidence included the high level of statistical heterogeneity among the studies analysed (I²=96% for pooled analysis of all studies and I²=89% for subanalysis of studies on early-onset infection). The studies also varied in how they defined neonatal sepsis, the age of the neonates assessed and the proportion of preterm neonates. The lack of information on the sources searched for this review and how they were assessed means that publication and reviewer bias are possible.

The heterogeneity of the evidence available on the use of serum procalcitonin concentration to diagnose neonatal sepsis at presentation prevents firm conclusions from being drawn on the value of this marker. This evidence is unlikely to have an impact on NICE CG149, which does not include any recommendations on using serum procalcitonin concentration as a diagnostic marker for neonatal sepsis.
Further research is needed on the approaches for ruling in and ruling out sepsis, such as serum procalcitonin concentration, in infants at risk of early-onset infection. This need is outlined in NICE research recommendation 4.4 - What is the clinical and cost effectiveness of laboratory investigations used individually or in combination to exclude early-onset neonatal infection in babies receiving antibiotics for suspected infection?

**Key reference**

### 1.6 Antibiotics for suspected infection

**Gentamicin dosing**

NICE CG149 recommends that intravenous benzylpenicillin with gentamicin should be the first-choice antibiotic regimen for empirical treatment of neonates with suspected infection. Gentamicin should be given in a starting dosage of 5 mg/kg (which the full version of NICE CG149 notes is to achieve a peak blood gentamicin concentration of 8 mg/litre). If a second dose of gentamicin is to be given, it should usually be given 36 hours after the first dose. The interval may be shortened, based on clinical judgement. Subsequent gentamicin doses and intervals should be decided taking account of blood gentamicin concentrations.

If a second dose of gentamicin is to be given, the trough blood gentamicin concentration should be measured immediately before giving the second dose. The gentamicin dose interval should be adjusted to achieve trough concentrations of less than 2 mg/litre. Repeating the measurement of trough concentrations should be considered immediately before every third dose of gentamicin, or more frequently if necessary. If the course of gentamicin lasts more than 3 doses, a trough concentration of less than 1 mg/litre is advised.

Healthcare professionals should consider measuring peak blood gentamicin concentrations 1 hour after starting the gentamicin infusion in selected babies.

Alshaikh et al. (2012) conducted a retrospective observational study to evaluate an extended interval dosing regimen of gentamicin in very preterm infants. The study recruited infants with a gestational age of 28 weeks or less who received gentamicin for suspected sepsis for at least 5 days from a single centre in Canada. A first 5 mg/kg dose of gentamicin was given on the first day of life. The timing of the second 5 mg/kg dose was based on gentamicin level at 22 hours:

- 1.2 micrograms/ml or less=second dose at 24 hours
- 1.3–2.6 micrograms/ml=second dose at 36 hours
- 2.7–3.5 micrograms/ml=second dose at 48 hours
- 3.6 micrograms/ml or more=hold next dose and repeat measurement of gentamicin level at 24 hours. Base dosing interval on time to achieve a level of less than 2 micrograms/ml.

The aim of this extended interval dosing regimen was to increase the proportion of patients who had gentamicin levels with a peak of 5–12 micrograms/ml and a trough of less than 2 micrograms/ml. Infants treated with this dosing interval were compared with a historical control group of infants who were born in the previous 6 months and who received 2.5 mg/kg gentamicin every 24 hours.

Among the 33 neonates treated according to 22-hour gentamicin levels, 20 received gentamicin at 36-hour intervals and 13 were on 48-hour intervals. The majority (91%) achieved the target peak and trough levels of gentamicin, with no significant difference between the 36-hour and 48-hour interval groups in the peak and trough levels. Compared with the historical control of 34 infants (who received 2.5 mg/kg gentamicin every 24 hours), infants treated according to 22-hour gentamicin levels had significantly higher peak
gentamicin levels (median 9.8 micrograms/ml compared with 4.6 micrograms/ml in controls, p<0.001). Trough gentamicin levels were similar in the 2 groups (median 1.1 micrograms/ml in the 22-hour group and 1.2 micrograms/ml in the control group). No neonate in either group had a blood culture positive for early-onset neonatal infection.

This study was limited by its small sample size and its non-randomised, retrospective design. In addition, 82% of infants who were treated according to 22-hour gentamicin levels had clinical and echocardiographic evidence of patent ductus arteriosus, which is associated with reduced renal clearance and may have mildly elevated trough gentamicin levels.

The evidence suggests that an extended dosing regimen of 5 mg/kg gentamicin every 36 or 48 hours according to blood gentamicin levels at 22 hours can achieve effective and safe peak and trough levels of gentamicin in very preterm babies. The evidence is unlikely to have an impact on NICE CG149 given that the guidance recommends considering a 5 mg/kg dose of gentamicin every 36 hours in term and preterm infants.

Key reference

1.7 Duration of antibiotic treatment

Serial C-reactive protein measurement

NICE CG149 recommends that C-reactive protein concentration should be measured at presentation when starting antibiotic treatment in babies with risk factors for infection or clinical indicators of possible infection. C-reactive protein concentration should be measured again 18–24 hours after presentation in babies given antibiotics. A lumbar puncture to obtain a cerebrospinal fluid sample should be considered in babies with a C-reactive protein concentration of 10 mg/litre or greater who did not have a lumbar puncture at presentation and are receiving antibiotics, if it is thought safe to do so.

Stopping antibiotic treatment at 36 hours should be considered in babies given antibiotics because of risk factors for infection or clinical indicators of possible infection if:

- the blood culture is negative, and
- the initial clinical suspicion of infection was not strong, and
- the baby’s clinical condition is reassuring with no clinical indicators of possible infection, and
- the levels and trends of C-reactive protein concentration are reassuring (which in the full version of NICE CG149 is referred to as improving towards the normal range [<10 mg/litre] at 18–24 hours compared with level at presentation).

A retrospective cohort study by Coggins et al. (2013) assessed the effect of consecutive testing of C-reactive protein concentration on duration of antibiotic use in preterm infants of very low birth weight. Data were analysed from a single centre in the USA on preterm infants who weighed less than 1500 g and who had negative blood cultures during the first week postpartum. C-reactive protein concentration was measured twice: at initial evaluation and at 48 hours. Antibiotic treatment should have been stopped within 48 hours in those who had normal C-reactive protein values (<10 mg/litre) at both time points and a negative blood culture at 48 hours. The primary outcome was the length of antibiotic treatment in infants treated on the basis of C-reactive protein values compared with the duration in infants not treated according to this protocol.

Of the 636 culture-negative infants identified, 569 had received empiric antibiotics in the first week postpartum for suspected early-onset sepsis. A total of 409/569 (72%) infants were treated on the basis of C-reactive protein values: antibiotics were discontinued at 48 hours in
311 infants with 2 normal C-reactive protein results and continued in 98 infants with at least 1 elevated C-reactive protein concentration (>10 mg/l). The remaining 160/569 (28%) infants had normal C-reactive protein results but continued to receive empiric antibiotics for more than 48 hours: these cases were considered non-compliant.

Infants treated according to C-reactive protein levels received a smaller total dose of ampicillin than those whose C-reactive protein values were not used to guide their treatment (median 520 mg/kg versus 1380 mg/kg, p<0.001). The rates of morbidities associated with prematurity were no higher in infants treated according to C-reactive protein levels, but the mortality rate was significantly lower (6/409 [1.5%] versus 14/160 [8.8%], p=0.003).

In a separate analysis of 308 infants with confirmed positive blood cultures, serial C-reactive protein values remained negative 38 (12%) infants.

Limitations of the evidence included the retrospective nature of the study and the lack of power in analyses of morbidities of prematurity. In addition, the lack of a comparison group in whom no C-reactive protein levels were taken meant that overall change in antibiotic use could not be measured.

The evidence suggests that antibiotic treatment could be safely stopped at 48 hours in culture-negative infants of very low birth weight who have C-reactive protein concentrations of less than 10 mg/litre at presentation and at 48 hours. This evidence supports the recommendation in NICE CG149 that closely-timed serial C-reactive protein measurements can be used to guide antibiotic treatment in infants at risk of early-onset neonatal infection and confirms the applicability of this approach in infants of very low birth weight.

Further research is needed on the effectiveness of laboratory investigations, such as C-reactive protein level, used individually or in combination to guide the decision to stop treatment in babies receiving antibiotics for early-onset neonatal infection (NICE research recommendation 4.4).

Key reference

1.8 Therapeutic drug monitoring for gentamicin
No new key evidence for this section was selected for inclusion in this Evidence Update.

1.9 Care setting
No new key evidence for this section was selected for inclusion in this Evidence Update.
2 New evidence uncertainties

No new evidence uncertainties were identified during the Evidence Update process. However, any uncertainties that may be identified in future for antibiotics for early-onset neonatal infection will be added to the UK Database of Uncertainties about the Effects of Treatments (DUETs). Other uncertainties can be found in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.
Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Antibiotics for early-onset neonatal infection. NICE clinical guideline 149 (2012)

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 September 2011 (the end of the search period of NICE clinical guideline 149) to 15 January 2014:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)
- PsycINFO

The Evidence Update search strategy replicates the strategy used by NICE CG149 (for key words, index terms and combining concepts) as far as possible. If this is not practical, then the search replicates the basic PICO (population, intervention, comparison, outcome) structure of the original searches. Where necessary, the strategy is adapted to take account of changes in search platforms and updated indexing language.

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above.

Figure 1 provides details of the evidence selection process. The list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

See the NICE Evidence Services website for more information about how NICE Evidence Updates are developed.
Table 1 MEDLINE search strategy (adapted for individual databases)

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Figure 1 Flow chart of the evidence selection process

- 7838 records identified through search
  - 1383 duplicates from searching
  - 6455 records after duplicates removed
    - 5679 records excluded at first sift
    - 776 records included after first sift
      - 594 records excluded at second sift
      - 182 records included after second sift
        - 154 records excluded at critical appraisal and evidence prioritisation
  - 28 records discussed by EUAG
    - 0 additional records identified by EUAG outside original search
      - 5 records included by EUAG in published Evidence Update
        - 23 records excluded by EUAG

EUAG – Evidence Update Advisory Group
Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who reviewed the prioritised evidence from the literature search and advised on the development of the Evidence Update.

Dr Mark Turner – Chair  
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