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Best Practices for the Diagnosis and Evaluation of Infants With Robin Sequence

A Clinical Consensus Report

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**IMPORTANCE**

Robin sequence (RS) is a congenital condition characterized by micrognathia, glossoptosis, and upper airway obstruction. Currently, no consensus exists regarding the diagnosis and evaluation of children with RS. An international, multidisciplinary consensus group was formed to begin to overcome this limitation.

**OBJECTIVE**

To report a consensus-derived set of best practices for the diagnosis and evaluation of infants with RS as a starting point for defining standards and management.

**EVIDENCE REVIEW**

Based on a literature review and expert opinion, a clinical consensus report was generated.

**FINDINGS**

Because RS can occur as an isolated condition or as part of a syndrome or multiple-anomaly disorder, the diagnostic process for each newborn may differ. Micrognathia is hypothesized as the initiating event, but the diagnosis of micrognathia is subjective. Glossoptosis and upper airway compromise complete the primary characteristics of RS. It can be difficult to judge the severity of tongue base airway obstruction, and the possibility of multilevel obstruction exists. The initial assessment of the clinical features and severity of respiratory distress is important and has practical implications. Signs of upper airway obstruction can be intermittent and are more likely to be present when the infant is asleep. Therefore, sleep studies are recommended. Feeding problems are common and may be exacerbated by the presence of a cleft palate. The clinical features and their severity can vary widely and ultimately dictate the required investigations and treatments.

**CONCLUSIONS AND RELEVANCE**

Agreed-on recommendations for the initial evaluation of RS and clinical descriptors are provided in this consensus report. Researchers and clinicians will ideally use uniform definitions and comparable assessments. Prospective studies and the standard application of validated assessments are needed to build an evidence base guiding standards of care for infants and children with RS.
Currently, no consensus exists regarding the diagnosis or evaluation of a newborn with Robin sequence (RS), a congenital condition occurring in approximately 1 in 8500 live births. The literature addressing RS has focused on the experience of single centers based on study-specific definitions. Multidisciplinary collaboration and prospective studies using similar definitions are required to advance care in RS. To further this goal, an international consensus meeting was convened in Utrecht, the Netherlands, from October 31 to November 1, 2014, at which 145 participants from 24 countries attended. An expert panel was convened to develop a RS clinical consensus report (CCR) based on synthesis of available literature and expert opinion. The objective of this article is to report the resulting consensus-derived set of best practices for the diagnosis and evaluation of children with RS as a starting point for defining standards and management.

Methods

The CCR was developed after the completion of 7 predetermined steps. These included (1) evaluation of the suitability of RS for a CCR, (2) panel selection and recruitment, (3) vetting of potential conflicts of interest, (4) a panel meeting to determine the CCR scope and focus, (5) a systematic literature review and generation of the CCR, (6) iterative revision of the CCR based on survey results, and (7) CCR review and agreement.

Determination of RS as the Topic of a Consensus Report, Panel Recruitment, and Vetting

Robin sequence was considered as a possible subject of a CCR based on discussions at a craniofacial meeting in 2013 (12th International Congress on Cleft Lip/Palate and Related Craniofacial Anomalies; May 10, 2013; Orlando; Florida). The consensus leadership (C.C.B., K.N.E., and P.H.) developed a panel of international consensus meeting faculty, with a strategic aim to cultivate participation from the pertinent specialty groups. The panel membership was surveyed to generate an agenda and specific objectives. Endorsements for the meeting were obtained from numerous societies and associations (http://www.robinsequence.nl/home.html). The panel, selected based on clinical and research expertise focusing on RS, contained representatives from pediatrics (K.N.E. and V.A.), sleep medicine (K.F.M.J.), neonatology (C.F.P.), genetics (H.M.S., M.H.V., and M.E.A.), plastic surgery (C.C.B., C.F., J.M., P.D.G., R.S., F.V.M., E.P., A.P., H.B., and M.V.C.), otolaryngology (P.H. and L.S.), maxillofacial surgery (M.M. and M.K.), developmental biology (P.G.F.), dentistry, and orthodontics (S.S. and P.A.M.). All members were vetted by the panel chair (C.C.B.), and no conflicts of interest were identified.

Literature Review and Determination of the Scope of the Consensus Report

The expert panel defined the scope and current controversies in diagnosing and evaluating children with RS during the international consensus meeting. Aiming to build a report that would identify gaps in evidence and prioritize clinical focus areas in RS care, the panel assembled topic-specific subgroups. The stepwise development of each report included a systematic literature review to identify up-to-date evidence focused on the designated topic. These topic areas were deliberated by the multidisciplinary subgroups at the international consensus meeting and subsequently used as the framework for developing the CCR.

Generation of Consensus Document

After the international consensus meeting, the panel divided into 6 groups, each with a designated group leader. The topics, agreed on by all conference attendees, included (1) micrognathia (M.M.), (2) glossoptosis (P.H.), (3) airway obstruction (K.F.M.J.), (4) feeding problems (V.A.), (5) cleft palate (R.S.), and (6) etiology (H.M.S.). The CCR was developed using software (http://www.projectplace.com) that allowed each group to collaborate and work concurrently. The respective groups devised initial drafts. The entire membership was then invited to provide comments and suggestions. Three members (C.C.B., K.N.E., and P.H.) integrated all documents into one CCR. All members were given another opportunity to review and edit the manuscript and make suggestions.

Clinical Consensus Report

Definition of RS

Consensus was reached that micrognathia is the primary characteristic of RS. Other mandatory diagnostic characteristics include glossoptosis and airway obstruction. Cleft palate is considered a common and additional feature. It was agreed on that management for all newborns with RS begins with assessing and treating airway obstruction (Table 1).

Micrognathia

Definition of Micrognathia

Several attempts have been made to define micrognathia. A cephalometry protocol by Pruzansky and Richmond investigates mandibular size and craniofacial growth in patients with RS. However, the limited 2-dimensional nature of these images and the difficulty in accurately positioning and immobilizing the awake infant that is required to obtain precise cephalograms reduce the usefulness of this method. Computed tomography (CT) can generate 3-dimensional reconstructed images; however, the additional risks of radiation exposure during infancy and the lack of normative CT data are shortcomings. Hence, for most clinicians, the diagnosis of micrognathia is largely subjective. The literature is ambiguous in regard to catch-up mandibular growth in infancy. Studies show...

Key Points

Question: What are the agreed-on clinical features of and evaluations for infants and children with Robin sequence?

Findings: In this consensus report and review, an international, multidisciplinary panel of clinical experts agreed that the diagnosis of Robin sequence can be made in children with micrognathia, glossoptosis, and upper airway obstruction. Gaps in evidence in this uncommon condition have limited advances in care and outcomes assessments in children with Robin sequence.

Meaning: Using uniform definitions and comparable assessments of the functional and phenotypic features has a global application and the potential to improve care and outcomes in this fragile population with Robin sequence.
themicrognathicmandibleinchildrenwithRSissmallandretrog-
натичthroughoutchildhoodandadolescence,withcharacteristic
morphological features, including deficiencies in the mandibular
bodyandramallengths,moreopengonialangle,andposteriorlyin-
clinichin.ManyindividualswithRSalsohaveupperjawhypopla-
sia.MandibularmorphologyandpositioninRSvarybasedonthespe-
cific diagnosis, the existence of mandibular hypodontia, and the
presenceofassociatedsyndromes.8,10

Assessment of Micrognathia
Theobjectiveevaluationofmicrognathiavariesdependingonthe
severity of clinical findings and available investigative and treat-
mentoptions. Mandibularsizecanbeassessedusingmultiplemo-
dalities,includingdeficienciesinthe mandibular
bodyandramalengths,more open gonial angle, and posteriorly in-
clinichin. Many individuals with RS also have upper jaw hypopla-
sia. Mandibular morphology and position in RS vary based on the spe-
cific diagnosis, the existence of mandibular hypodontia, and the
presenceofassociatedsyndromes.8,10

Assessment of Micrognathia
The objective evaluation of micrognathia varies depending on the
severity of clinical findings and available investigative and treatment
options. Mandibular size can be assessed using multiple modalities, including low-dose multissection CT, cone beam CT, lateral
cephalograms, plaster casts, 3-dimensional photography, and di-
rectmeasurementswithrulersandcalipers.Access tothesemodal-
tiesvaries,andnocriterionstandardmethodexists to diag-
nose, characterize, and monitor micrognathia. The optimal tool to
measure micrognathia during childhood should be widely avail-
able, reproducible, and cost-effective. The Jaw Index is a simple, in-
personmeasurethatmayfulfillsomeoftheserequirements
(Figure).11 The advantages of the Jaw Index are its simplicity, usabil-
ity, and potential application to early screening and characteriza-
tion of micrognathia in newborns. However, the Jaw Index may not
reflect functional airway compromise, and validation of this tool in
multiplepopulationsisneededbeforeadoption.12,13

**Glossoptosis**

**Definition of Glossoptosis**
Glossoptosis is a dynamic clinical entity defined as displacement of
the tongue base into the oropharynx and hypopharynx. The de-
gree of glossoptosis and resultant upper airway obstruction can vary.
Inseverecases, the child will have inspiratory stertor or stridor with
increased respiratory effort, possibly accompanied by apnea and cya-
notic episodes. Children with mild glossoptosis may maintain an ade-
quenearwaywhenawake,suckings on a pacifier, or crying but have
ahighermentedfor sleep-disordered breathing(SDB).14 It is un-
clear whether the size of the tongue is consistent across the phe-
notypic spectrum of RS, and there is no definitive correlation be-
tween the degree of micrognathia and severity of glossoptosis.15 The
findings of an electromyography study16 also suggest the presence
of abnormal neuromuscular tone of the tongue in RS.
Assessment of Gingssoptosis
Intraoral examination of the infant with glossoptosis may reveal a
minimally visible, posteriorly positioned tongue, occasionally pulled
up into a palatal cleft (eFigure 1 in the Supplement). While no crite-
rion standard test exists to diagnose glossoptosis, at minimum, en-
doscopy allows for visualization of the tongue position in the oral
cavity and oropharynx. Although some physicians prefer a tran-
soral approach with a flexible endoscope, nasopharyngolaryngos-
copy may be required to obtain a holistic view of the oropharyn-
geal region. Endoscopy can identify additional levels of airway
narrowing other than at the tongue base, which is essential for de-
termining optimal management.17 There are reports of using endo-
scopic images to further localize and categorize the oropharyngeal
obstruction and to grade the severity of airway compromise.18,19
However, this technique is difficult to reproduce in the crying, awake
infant, and small endoscopes produce less optimal image resolu-
tion. Also, respiratory problems primarily occur when a child with
RS is relaxed or sleeping, especially when positioned supine. Dur-
ing nasopharyngolaryngoscopy, the awake child is often agitated,
resulting in muscular tension, and the endoscopic characteristics
may not mimic the crucial moments when obstruction occurs. Radi-
ographic studies are considered to be of limited value and are not rou-
tinely used to diagnose glossoptosis. Newer dynamic imaging tech-
niques, such as cine magnetic resonance imaging and multidetector
CT, can better delineate and quantify the degree of obstruction at
various sites in the upper airway but are not universally available and
require the patient to be cooperative or intubated.20,21

Respiratory Problems Due to Upper Airway Obstruction
Definition of Respiratory Problems
Glossoptosis is the primary cause of respiratory problems in RS
(eFigure 2 in the Supplement), although multiple factors will influ-
ence a child’s respiratory status. Associated with considerable mor-
bidities affecting health, growth, and development, the recognition
and treatment of respiratory problems are essential.22–26 The spec-
trum of respiratory compromise in RS is broad. Sleep-disordered
breathing is a complex phenomenon of upper airway dysfunction
during sleep and is characterized by snoring or increased respiratory ef-
fort due to upper airway resistance and pharyngeal collapsibility. Ob-
structive SDB includes a spectrum of clinical entities, including primary
snoring, upper airway resistance syndrome, obstructive hypoventi-
lation, and obstructive sleep apnea (OSA) syndrome.

Assessment of Respiratory Problems
The respiratory assessment in RS begins immediately after birth, al-
though symptoms of respiratory compromise may develop over time.
The intermittent nature of upper airway obstruction may lead to a de-
lay in diagnosis and referral to a specialized team. While infants with
life-threatening respiratory distress require direct respiratory sup-
port, most infants with RS can be observed clinically. Clinical signs of
respiratory compromise in infants with RS include stertor or stridor,
labored breathing, diaphoresis, apnea, and restlessness and can be
assessed during sleep, in wakefulness, and with feeding.27,28 Posi-
tioning the child in a prone or lateral decubitus position will help to
determine whether airway obstruction can be lessened. A jaw thrust
maneuver pulls the tongue forward and is a tool that helps to illus-

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Table 2. Overview of Criteria for Respiratory Compromise and Obstructive Sleep Apnea in Infants With Robin Sequence

<table>
<thead>
<tr>
<th>Source</th>
<th>Oximetry Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>van den Elzen et al, 40, 2001</td>
<td>Repeated SaO₂ &lt;90%</td>
</tr>
<tr>
<td>Wagener et al, 40, 2003</td>
<td>SaO₂ &lt;90% saturation for &gt;5% of 24 h or SaO₂ &lt;80%</td>
</tr>
<tr>
<td>Breugem et al, 43, 2008</td>
<td>SaO₂ &lt;93% for &gt;5% total sleep time</td>
</tr>
<tr>
<td>Pradel et al, 42, 2009</td>
<td>Repeated cyanotic episodes and respiratory adaptation disorder</td>
</tr>
<tr>
<td>Bacilio et al, 45, 2011</td>
<td>Single SaO₂ value &lt;80% during sleeping, feeding, or wakefulness</td>
</tr>
<tr>
<td>Rogers et al, 44, 2011</td>
<td>SaO₂ consistently &lt;90%</td>
</tr>
<tr>
<td>Abel et al, 45, 2012</td>
<td>Mild is 3 clusters of desaturation with at least 3 dips &lt;80%, moderate is 3 dips &lt;85%, and severe is 3 dips &lt;80%</td>
</tr>
</tbody>
</table>

Table 3. Cleft Palate Classifications

<table>
<thead>
<tr>
<th>Classification by Jensen et al, 55</th>
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</thead>
<tbody>
<tr>
<td>0 Subnasal cleft palate</td>
</tr>
<tr>
<td>1 Soft palate only</td>
</tr>
<tr>
<td>2 Soft palate and less than one-third hard palate</td>
</tr>
<tr>
<td>3 Soft palate and greater than one-third but less than two-thirds hard palate</td>
</tr>
<tr>
<td>4 Complete: soft and hard to incisive foramen</td>
</tr>
</tbody>
</table>

LAHSHAL code

Length: from Randall et al, 56

Measurements of the extent of the cleft at the time of surgery

Minimum to be measured: width at hard or soft palate junction with calipers at the time of surgery, both soft-tissue width and bony width

For investigation: methods by Godbout et al, 54 and Filho et al, 57

Shape: U-shaped or V-shaped

Photograph at the time of palate repair (with mirror)

Impression and model

Abbreviation: LAHSHAL indicates lip (right), alveolus (right), hard palate, soft palate, hard palate, alveolus (left), lip (lip).

Feeding Problems

Definition of Feeding Problems

A spectrum of feeding problems in RS exists, which can be categorized into prolonged feeding times, reduced oral intake, unsafe oral feeding, and precipitation of respiratory compromise. We propose that feeding disorders in infants with RS can be defined as the inability to take in adequate oral feeds efficiently to support normal growth (eg, >30 minutes with 1 bottle feed) or oral feeding that potentiates airway or respiratory compromise (eg, worsening airway obstruction and aspiration).

Successful feeding depends on a chain of complex, rhythmically coordinated, successive movements: suction is followed by swallowing, intermittently by breathing. Factors contributing to feeding problems in RS include the anatomic tongue position, upper airway obstruction, oropharyngeal dysfunction, and weak sucking mechanics, compounded by nasal regurgitation and difficulty generating adequate negative intraoral pressure with palatal clefting. In addition, central or neuromotor disabilities may affect sucking and swallowing coordination, and feeding impairment is anticipated in children with RS and specific syndromes and genetic conditions. Aspiration can result from disordered suck-swallow-breath or primary swallowing dysfunction. Tachypnea and increased work of breathing negatively affect feeding mechanics and potentiate gastroesophageal reflux. Reflux-induced secretion production and airway inflammation disrupt the feeding-respiratory balance. Feeding problems may worsen during the first weeks of life and tend to improve from 4 months through the first year of life.

Assessment of Feeding Problems

Given the association with failure to thrive, swallowing dysfunction, and developmental delays, the recognition and treatment of feeding problems in RS are priorities. A clinical feeding assessment performed by experienced health care professionals in the first days and weeks of life will include evaluations of (1) quality of bottle feeding and feeding time, (2) effect of feeding on respiratory status, and (3) quality of weight gain and growth (expressed as the standard deviation for weight or weight gain). Complementary feeding investigations can help diagnose swallowing problems and guide therapeutic interventions. Fiber-optic endoscopic evaluation, videofluoroscopy, swallowing electromyography, and esophageal manometry have been described; however, there is no consensus regarding the validity and interpretation of these investigations in infants with RS. Infant feeding specialists are valuable in delineating unique feeding problems. It is essential to define feeding problems together with parents and feeding experts as early as possible.

Etiological Diagnosis

Thorough assessment by a pediatrician and a clinical geneticist is advised for all children with suspected RS, with reassessment because a syndrome may become apparent at a later age. When patients have a co-occurring syndrome, such as Stickler syndrome, RS with Stickler syndrome is an appropriate diagnostic description. Because RS occurs as an isolated condition or as part of a syndrome or multiple-anomaly disorder, the diagnostic process in each context differs. Micrognathia is the hypothesized initiating event in RS. However, micrognathia may be caused by multiple different etiologies. The OMIM catalog lists 483 genetic disorders in which micrognathia is a clinical component,
and POSSUMweb lists 1080 genetic and teratogenic disorders with micrognathia.67 The presence of additional anomalies suggests the possibility of an associated syndrome. In one series of 117 individuals with RS, 48% had isolated RS, 35% had identifiable syndromes, and 17% had RS presumed to be caused by a unique or unidentified syndrome.68 In a 2012 analysis of genetic diagnoses in 125 patients with RS, 58% had associated syndromes, most commonly Stickler and Marshall syndromes.67 Provision of a genetic diagnosis to a child and family has substantial effect on long-term management, including surveillance recommendations, perioperative precautions, and additional health care needs. Table 4 summarizes the comprehensive examination and assessments of etiology for infants with RS. In addition, an echocardiogram is recommended if 22q11.2 deletion is suspected or if there is a murmur, with brain magnetic resonance imaging if there is abnormal muscle tone, fetal akinesia, arthrogryposis, or microcephaly, as well as skeletal radiographs for any child with RS who is suspected to have a skeletal dysplasia. Radiographs of the scapula, ribs, and long bones may help identify anomalies associated with genetic lesions around the SOX9 gene.69,70 Ultimately, it may not be possible to advance the diagnosis beyond the concept of RS plus, in which the affected individual has RS with 1 or more additional anomalies that do not constitute a recognizable syndrome.

Summary and Future Directions

This CCR provides the basis and framework for the minimum assessment that is recommended for children with RS based on the opinions of a carefully chosen expert panel. Future consensus meetings will focus on measuring outcomes and identifying platforms for collaboration. Infrastructure development for standardized data collection and sharing is needed to build the evidence base that will inform future clinical practice guidelines.

Micrognathia

Currently, the diagnosis of micrognathia is largely subjective, and future studies should be conducted to define objective parameters. Reference guides for “normal” mandibular dimensions within various age, sex, and racial/ethnic groups have the potential for clinical application, may be useful in monitoring facial growth, and will help answer clinically important questions regarding the severity of the small mandible and mandibular catch-up growth in children with RS.

Glossoptosis

A careful physical examination with endoscopy is necessary to make the definitive diagnosis of glossoptosis. Currently, there are no objective parameters to describe glossoptosis severity. Future research should address 4 questions. First, is the tongue size, anatomy, and attachment to the mandible normal in children with RS? Second, is the tongue malposition related to poor neuromuscular control? Third, what is the role of newer dynamic imaging modalities in the workup of glossoptosis? Fourth, are there other contributing features, such as increased intrathoracic negative pressure?

Respiratory Problems

No widely accepted criteria exist to classify respiratory compromise in infants with RS. There is a scarcity of data concerning long-term follow-up after airway treatment. Treatment efficacy is measurable when the same evaluation methods are used before and after an intervention in similar populations. In principle, treatment should be guided by clinical symptoms and available tests. Centers treating patients with RS will ideally have access to comprehensive respiratory evaluations, including overnight laboratory PSG. Simple, accessible tools that reliably diagnose respiratory problems in RS in the clinical and home settings will be useful. Home respiratory polygraphy in children may be a promising diagnostic tool.71 Telemonitoring and wearable home monitoring recorders warrant further study. Ideally, the tools and decision-making thresholds will be integrated into a respiratory treatment algorithm.

Cleft Palate

Clear phenotypic description of the cleft palate should be collected for all infants with RS. Collection of photographs or dental models can allow for independent blind assessment of the cleft and address reliability limitations. Cleft phenotypic information will help determine which, if any, methods of describing the extent of the cleft are most predictive of outcome.

Feeding Problems

Integration of parents’ perception of feeding challenges and success will be useful in evaluating feeding in RS. Feeding assessments will ideally measure phenotype, oropharyngeal function, and standard feeding outcomes. Evaluations to consider with a research program include systematic assessment of feeding behaviors in infancy,72 cervical auscultation during feeding, esophageal manometry, and swallowing electromyography.

Table 4. Comprehensive Assessment of the Etiology of Robin Sequence

| Complete medical history and maternal history | Focus attention on any teratogenic exposures, including medications, tobacco, and alcohol |
| 3-Generation family history (pedigree) | Establish any history of similarly affected individuals, infant death, eye or vision problems, intellectual disabilities and developmental delays, and mode of inheritance if possible |
| Physical examination of the child | Include growth parameters, comprehensive dysmorphology assessment, and skeletal evaluation looking for skeletal dysplasias (eTable in the Supplement) |
| Physical assessment of both parents performed by a clinical geneticist | May identify microform cleft features, bifid uvula, micrognathia, or other features of a specific syndrome with variable phenotypic expression |
| Ophthalmologic examination | Check for the ocular features of Stickler syndrome during the neonatal period and 6 to 12 mo later in all infants with Robin sequence |
| Cytogenetic and/or molecular genetic investigations | Are recommended for children with Robin sequence and other congenital anomalies. Chromosomal disorders are common in children with multiple congenital anomalies, for whom chromosomal analysis or single-nucleotide polymorphism microarray is indicated. Although 22q11.2 deletion syndrome is an uncommon cause of Robin sequence, testing for 22q11.2 microdeletion can be considered, particularly in the presence of cardiac or renal anomalies, dysphagia, or hypocalcemia. Genetic testing for Stickler syndrome targeting the collagen genes (COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, COL9A3) can be performed |
| Longitudinal follow-up by a clinical geneticist | Identify syndromic diagnoses that may become apparent later in childhood |
Etiological Diagnosis

There are thousands of single-gene disorders, many of which are exceedingly rare or possibly unique. While making a genetic diagnosis is challenging for many infants with RS, next-generation sequencing technologies allow for identification of rare disorders and may be informative in RS. Clinical whole-exome sequencing has led to the diagnoses in up to one-third of individuals who had not received a diagnosis with other methods and will continue to be applied in research settings.

Conclusions

The diagnosis of RS can be made in children when there is micrognathia, glossoptosis, and upper airway obstruction. Using uniform definitions and comparable assessments of the functional and phenotypic features is a necessary first step in creating an evidence base. Prospective studies and the standard application of validated assessments will be necessary to guide standards and best practices for infants and children with RS. Research defining objective parameters on how we describe and compare these criteria will fill a large gap. Well-designed, prospective studies should also consider (1) engagement of parent stakeholders and (2) development of data standards for phenotypic, functional, and clinical descriptions. Comprehensive phenotypic and genetic investigations combined with a systematic severity classification have the potential to both guide care and facilitate outcome studies needed to advance care in RS. Collaboration will be essential to the progress in this rare yet important condition with lifelong effects on health and quality of life.

REFERENCES


Consensus Recommendation for Management of Infants With Robin Sequence

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