Literature review

Inherited bone marrow failure syndrome "Shwachman-Diamond Syndrome"

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Bone marrow plays a crucial role in the process of hematopoiesis, responsible for forming blood cells in the human body. When abnormalities occur in the bone marrow, they can have far-reaching implications for various types of blood cells. Bone marrow failure, a condition characterized by a malfunction in blood cell production, can result from either acquired factors later in life or genetic abnormalities. Inherited Bone Marrow Failure Syndromes (IBMFS) represent a rare category of genetic disorders. The apparent scarcity of reported cases may be attributed to misdiagnoses or the misclassification of other diseases when individuals with these conditions seek medical attention. Patients receiving an initial diagnosis of acquired aplastic anemia or cancer may, in fact, belong to this group of disorders. Understanding IBMFS requires carefully reviewing their clinical characteristics, laboratory investigations and appropriate management strategies. Healthcare professionals should be vigilant in recognizing potential cases to avoid misdiagnoses and ensure timely and accurate interventions for patients with these IBMFS.

The pathophysiology of IBMFS is rooted in abnormalities affecting the development of red blood cells, white blood cells and platelets from the bone marrow to the bloodstream. This leads to conditions such as aplastic anemia, low white blood cell count and/or low platelet count. While patients with IBMFS exhibit deficiencies in blood cell production, the severity of these abnormalities varies among different subtypes within this group.

Human blood hierarchy

Traditionally, generating blood involves a sequential process starting from stem cells and progressing through oligopotent progenitors,[1] which gradually become more specialized to unipotent progenitors. The presence of oligopotent cells is crucial in the established model of blood cell differentiation as they delineate the pathway from stem cells to unipotent progenitors.[2,3] In 2016, Notta, et al. introduced a novel cell-sorting approach to distinguish myeloid (My), erythroid (Er) and megakaryocytic (Mk) fates in individual CD34+ cells which has mapped the hierarchy of progenitors throughout human development.

During fetal development, the fetal liver exhibits a significant presence of distinct oligopotent progenitors with intertwined My, Er and Mk fates. Surprisingly, in adult bone marrow, the number of oligopotent progenitor intermediates remains limited, with multipotent and unipotent progenitors prevailing. Notably, Er-Mk lineages now have emerged from multipotent cells. This shift in developmental hierarchy challenges the existing belief and introduces a new perspective for comprehending both normal and pathologic conditions in human hematopoiesis.[4]

A redefined model of human blood development with a two-tier hierarchy in adulthood: a top-tier containing multipotent cells and a bottom-tier composed of committed unipotent progenitors. This study provides crucial insights into the complexity of the first major lineage bifurcation step in blood differentia-

tion, challenging earlier assumptions. The implications extend to molecular-level lineage specification, as markers associated with megakaryocytic, erythroid and myeloid differentiation show distinct expression patterns in human hematopoietic stem cells. This molecular heterogeneity challenges traditional models of lineage commitment.[4]

The GATA-1 positive Mk-Er committed progenitors in the stem cell compartment, suggesting that MEPs are derived from multipotent cells. In the murine bone marrow niche, a significant portion of LT-HSCs lies adjacent to Mks, playing a dual role in regulating HSC. Mks preserve the quiescent nature of LT-HSCs under normal conditions, while after myeloablation, they secrete growth factors, temporarily abrogating this effect and permitting HSC expansion. This direct differentiation of Mks from HSCs may regulate blood stem cell functionality in the niche. The first major bifurcation step in blood differentiation appears more complex than the simple segregation of myeloid and lymphoid lineages. Among humans, this step splits the Mk-Er lineage from the myelomonocytic lineage co-segregating with the lymphoid fate.[4] Investigating why the myelomonocytic lineage, but not the granulocytic lineage, is tied to the lymphoid fate comprising a critical area for future research.

Introduction to Inherited Bone Marrow Failure Syndromes

The manifestations may result in either pancytopenia, where all three types of blood cells are diminished, as seen in Fanconi anemia (FA) and Shwachman-Diamond Syndrome (SDS) or single cytopenia, where only one type of blood cell is reduced. Examples include severe congenital neutropenia with low levels of neutrophils, Diamond-Blackfan Anemia (DBA) with decreased red blood cells and thrombocytopenia with absent radii presenting with reduced platelets.

The inheritance patterns in the group of IBMFS can be sporadic, autosomal recessive, autosomal dominant or X-linked recessive. Extensive research has been conducted to identify genes associated with developing these diseases, and many relevant genes have been used to diagnose these conditions. Nevertheless, there remains a considerable number of patients in whom no genetic abnormalities related to IBMFS are detected during testing and these individuals may lack both clinical characteristics and clear laboratory findings associated with this group of diseases.

Key clinical features observed among patients with IBMFS include those detailed below.

1) Manifestations and symptoms of bone marrow failure
2) Identification of congenital anomalies or birth defects
3) Increased risk of developing cancer, along with a family history of cancer predisposition

Despite advancements in genetic research, some patients within the IBMFS group do not exhibit detectable genetic abnormalities related to these conditions. Additionally, these individuals may lack distinct clinical features and clear laboratory results associated with IBMFS.

Genetic disorders within the group of inherited bone marrow failure syndromes (IBMFS) include:

Presented with pancytopenia (Low Counts of All 3 Types of Blood Cells)

- Fanconi anemia (FA)
- Shwachman-Diamond syndrome (SDS)
- Dyskeratosis congenita (DKC)
- Congenital amegakaryocytic thrombocytopenia (CAMT)

Presented with anemia

- Diamond-Blackfan anemia (DBA)

Presented with neutropenia (low white blood cell count especially neutrophils)

- Severe congenital neutropenia (SCN)

Presented with thrombocytopenia (Low Platelet Count)

- Thrombocytopenia with absent radii (TAR)

These genetic disorders manifest as bone marrow failure syndromes and are characterized by various combinations of pancytopenia, anemia, neutropenia and

thrombocytopenia. Each disorder within these groups may exhibit distinct clinical features and genetic abnormalities, contributing to the complexity of the IBMFS. This article will focus only on SDS.

Shwachman-Diamond Syndrome

SDS, also known as Shwachman-Bodian-Diamond Syndrome (SBDS) or congenital lipomatosis of the pancreas, is a rare genetic disorder belonging to the group of IBMFS. The syndrome is characterized by abnormalities in bone marrow function, exocrine (PI) (reduced enzyme secretion from the pancreas) and anomalies in the skeletal structure. Additionally, reports indicate abnormalities in other organs such as the liver, kidneys, teeth and the immune system. An increased risk has been observed of developing diseases such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).[5]

SDS was first described by Harry Shwachman, an American pediatrician and Martin Diamond, a pediatric radiologist, in 1964.[5] They reported a group of patients presenting PI, bone marrow dysfunction and metaphyseal chondrodysplasia (abnormal development of the long bones). In 2003, researchers identified mutations in the SBDS gene as the primary cause of SDS.[6] The SBDS gene provides instructions for making a protein involved in the maturation of ribosomes, essential cellular structures for protein synthesis. The SBDS gene mutations lead to a shortage of functional SBDS protein, affecting ribosome maturation and potentially disrupting various cellular processes. This cellular dysfunction contributes to the multisystemic features observed in SDS.

SDS is typically diagnosed between 1 and 3 years of age, with a male-to-female ratio of 1.7 to 1. Although comprising a rare condition, it ranks second in prevalence among exocrine PI disorders, following cystic fibrosis and third among IBMFS, after FA and DBA.[7] The exact mechanism linking gene defects and the bone marrow-related features of SDS are not fully understood. Studies have suggested abnormalities in cell growth when normal CD34 cells are cultured on stroma from patients with SDS.[8] This may indicate that the defect lies in the stroma. Additionally, increased angiogenesis (formation of new blood vessels) in the bone marrow stroma of these patients may be related to the elevated risk of developing blood-related disorders and leukemia.

Genetically, SDS follows an autosomal recessive inheritance pattern. The SBDS gene, located on chromosome 7q11, consists of 5 exons and encodes a protein with approximately 250 amino acids. Mutations in the SBDS gene, mostly occurring on exon 2, often result in forming a pseudogene (SBDSP). Various types of mutations such as missense, nonsense, frameshift, splice site defects, insertions and deletions have been identified. The genotype-phenotype relationship in SDS is not well-established.

Research suggests that the SBDS protein may be involved in RNA processing and/or ribosome biogenesis. The telomeres of SDS mononuclear cells are shorter on average than those of normal mononuclear cells, indicating a potential connection to abnormalities in hematopoiesis, increased apoptosis and malignant transformation. Clinical and laboratory manifestations of SDS include neutropenia (low levels of neutrophils), anemia (usually normochromic normocytic) and thrombocytopenia (low platelet count). The severity can vary and patients may remain asymptomatic. Multilineage cytopenia, affecting all three blood cell types, has been observed in a subset of patients.[9-11]

Clinical features and laboratory findings

Hematologic manifestations Neutropenia, specifically of the neutrophil type, is the most common hematologic abnormality observed in SDS, occurring in up to 88 to 100% of patients. Neutropenia may present as chronic, intermittent or cyclic. Intermittent neutropenia is the most prevalent form. Aside from reduced neutrophil counts, these patients often experience impaired neutrophil functions such as migration and chemotaxis[12]. As for anemia, approximately 80% of patients exhibita-

symptomatic normochromic normocytic red blood cells, with some cases showing larger red blood cells. Additionally, hemoglobin F levels are elevated in 80% of patients. Low platelet count (thrombocytopenia) is found in 24 to 88% of cases, with 10 to 65% of patients experiencing pancytopenia.[13]

Pancreatic dysfunction and liver disease Exocrine PI, characterized by reduced enzyme secretion, is a significant finding in SDS. Additional laboratory tests may reveal abnormalities in quantitative pancreatic stimulation tests, decreased levels of cationic trypsinogen in the blood and irregularities in the 72-hour fecal fat analysis. Pancreatic lipomatosis may also be detected using ultrasound, magnetic resonance imaging (MRI), or computerized tomography (CT) scan. Steatorrhea (fat in the stool), malabsorption and failure to thrive are common. However, about 50% of patients show improved liver function. Skeletal anomalies including short stature and metaphyseal dysostosis are frequently observed, often at the femoral head. Furthermore, 50 to 75% of patients may exhibit hepatomegaly or increased liver enzyme levels, with improvement often seen with age.[5] Hepatomegaly is a prevalent occurrence among young children receiving a diagnosis of SDS. Elevated levels of liver enzymes in the serum are observed in up to 75% of patients, predominantly among infants and young children and these elevated levels tend to diminish with age. Limited longitudinal data suggest that liver disease associated with SDS does not result in significant long term clinical consequences. In recent series, no cases of chronic liver disease have been reported among individuals with SDS.[14]

Nutritional involvement The average birth weight for individuals with this condition falls within the 25th percentile. Growth failure, accompanied by malnutrition, is a common occurrence in the initial year of life, especially before a diagnosis is confirmed. Multiple factors contribute to this, such as insufficient nutrient intake, feeding challenges, PI and recurrent infections. By the time children reach their first birthday, more than one half of the patients have fallen below the 3rd percentile for both height and weight. Following a diagnosis and appropriate treatment, most children exhibit a normal growth trajectory, yet they consistently remain below the 3rd percentile for both height and weight[15].

Other manifestations Additional manifestations involving skeletal issues include skeletal dysplasia and low-turnover osteoporosis. Skeletal dysplasia is characterized by metaphyseal changes in the long bones and costochondral junctions. Less common bone anomalies such as supernumerary fingers and syndactyly, have been observed. In a limited cohort, all individuals displayed evidence of metaphyseal dysplasia at some point, although the frequency and development rate are currently unknown. Delayed permanent teeth eruption, dental dysplasia, an increased susceptibility to dental caries and periodontal disease represents potential oral manifestations. Rarely, there have been reports of abnormalities affecting the kidneys, eyes, skin, testes, endocrine pancreas, heart, nervous system and craniofacial structures.[16]

How do we diagnose SDS?

Most individuals typically exhibit signs of growth failure, feeding difficulties and recurrent infections during infancy. While clinical diagnosis is commonly established in the early years of life, instances have occurred where the diagnosis may be confirmed among older children or even adults. The clinical diagnosis involves documenting evidence of characteristic exocrine pancreatic dysfunction and hematologic abnormalities and excluding known causes of exocrine pancreatic dysfunction and bone marrow failure.[12]

Special attention is directed towards ruling out cystic fibrosis, which is the most prevalent cause of PI, using a sweat chloride test. Other conditions such as Pearson disease characterized by PI and cytopenia and cartilage hair hypoplasia presenting diarrhea, cytopenia and metaphyseal chondrodysplasia are also considered. Additionally, IBMFS such as dyskeratosis congenita are included in the differential diagnosis.[12,17]

Exocrine pancreatic phenotype The clinical diagnosis of the exocrine pancreatic phenotype in SDS presents challenges due to the limited sensitivity and specificity of most pancreatic function tests. Complicating matters further, nearly one half of individuals with SDS demonstrate improved exocrine pancreatic function with age. A loss of 98% of exocrine pancreatic reserve must occur before signs of maldigestion become evident. Consequently, 72-hour fecal fat balance studies may appear normal despite a significant defect in pancreatic acinar function.[18]

The terms PI and pancreatic sufficiency (PS) distinguish individuals with PI, requiring pancreatic enzyme supplements with meals, from those with PS, exhibiting loss of pancreatic reserve without clinical evidence of maldigestion. Serum pancreatic enzyme concentrations, specifically low serum immunoreactive trypsinogen concentrations (< 6 μg/L) among patients with SDS with PI, are useful markers. However, among patients with PS, serum trypsinogen concentrations are usually above 6 μg/L, with one-fifth falling within the reference range. A low serum trypsinogen is indicative of the pancreatic phenotype, but a normal value does not exclude impaired exocrine pancreatic function[5,7,12].

Conversely, serum pancreatic isoamylase activities among patients with SDS are consistently low across all ages, irrespective of pancreaic status or trypsinogen concentration. However, serum isoamylase activity alone cannot serve as a sole marker due to age-dependent postnatal development. Serum trypsinogen, isoamylase and age have been incorporated in a diagnostic rule using Classification and Regression Tree (CART) analysis to effectively distinguish control individuals from those with a confirmed clinical diagnosis of SDS, excluding individuals under three years of age.[18]

Noninvasive approaches to evaluate or exclude pancreatic dysfunction include multi-dimensional imaging (ultrasound, CT or MRI) to assess fatty replacement of the pancreas. Fecal enzyme concentrations of pancreatic elastase or chymotrypsin may also be considered. Fecal elastase concentrations below 200 μg/g stool suggest severe pancreatic dysfunction, while concentrations below 100 μg/g indicate maldigestion due to exocrine PI. Fecal fat balance studies offer direct evidence of malabsorption severity but do not specify a pancreatic cause when fat malabsorption is detected[5].

While a “gold standard” method involving intestinal marker perfusion to directly measure pancreatic secretion during hormonal stimulation provides valuable insights in exocrine pancreas pathophysiology, its complexity and invasiveness limit its role in research studies. Alternative non-quantitative methods of collecting secretions such as aspiration with a duodenoscope or single-lumen duodenal tube, are not recommended due to considerable test variability, potentially misclassifying 25% of subjects with PS and low pancreatic reserve as having PI.[19]

Hematologic phenotype The hematologic phenotype in SDS is primarily characterized by intermittent or persistent neutropenia, often accompanied by cytopenias in other blood cell lineages. Additional typical findings include red blood cell macrocytosis, elevated hemoglobin F and varying degrees of marrow hypoplasia. Chromosome breakage studies using diepoxybutane or mitomycin C are recommended to rule out FA, unless the history, physical examination and initial work-up are indicative of SDS.[20]

For the initial evaluation of the hematologic phenotype, bone marrow aspiration and biopsy are essential, involving assessing the cellularity, differential, iron stain and cytogenetics. A bone marrow cytogenetic finding of i(7q) or del(20q) is highly associated with SDS. Virology studies such as the Epstein-Barr virus, cytomegalovirus and B19 parvovirus, may be pursued as clinically indicated to exclude other causes of bone marrow suppression and failure to thrive.[13]

When skeletal abnormalities co-exist with hematologic or pancreatic issues, they strongly suggest SDS. SDS bone dysplasia is characterized by short stature, delayed appearance but subsequent normal development of secondary ossification centers and variable meta-

Table 1. Clinical and molecular diagnostic criteria and treatment options[18]

Diagnostic Criteria
Clinical diagnosis
Fulfill the combined presence of hematological cytopenia of any given lineage (most often neutropenia) and exocrine pancreas dysfunction
Hematologic abnormalities may include
a. Neutropenia < 1.5 x10^9/L on at least 2 occasions over at least 3 months
b. Hypoproductive cytopenia detected on 2 occasions over at least 3 months
Tests that support the diagnosis but require corroboration
a. Persistent elevation of hemoglobin F (on at least 2 occasions over at least 3 months apart)
b. Persistent red blood cell macrocytosis (on at least 2 occasions over at least 3 months apart), not caused by other etiologies such as hemolysis or a nutritional deficiency
Pancreatic dysfunction may be diagnosed by the following
a. Reduced levels of pancreatic enzymes adjusted to age (fecal elastase, serum trypsinogen, serum (iso)amylase, serum lipase)
Tests that support the diagnosis but require corroboration
a. Abnormal 72 hr fecal fat analysis
b. Reduced levels of at least 2 fat-soluble vitamins (A, D, E and K)
c. Evidence of pancreatic lipomatosis, e.g., ultrasound, CT, MRI, or pathologic examination of the pancreas by autopsy)
Additional supportive evidence of SDS may arise from
a. Bone abnormalities
b. Behavioral problems
c. The presence of a first degree-family member diagnosed before with SDS
Other causes of pancreatic insufficiency should be excluded, in particular when the *SBDS* gene mutation analysis is negative
Molecular diagnosis: biallelic *SBDS* gene mutation
Positive genetic testing for *SBDS* mutations known or predicted to be deleterious, e.g., from protein modelling or expression systems for mutant SBDS

physeal widening and irregularity. These features are most often observed in the ribs during early childhood and in the proximal and distal femora later in childhood and adolescence. In severe cases, skeletal involvement may lead to generalized bone abnormalities. Although metaphyseal changes may become undetectable and clinically insignificant over time, progression can result in limb deformities, particularly at the hips and knees or stress fractures of the femoral necks.[21]

Additional clinical findings in SDS include short stature with or without malnutrition, as well as hepatomegaly with mild to moderate biochemical abnormalities of the liver, commonly observed among infants and young children with SDS. The clinical and molecular diagnosis criteria for the diagnosis of SDS is showed in Table 1.

Surveillance

Surveillance for SDS involves specific protocols depending on the clinical presentation. In cases with severe pancytopenia, bone marrow aspirate, biopsy and cytogenetic examination are deemed necessary. However, the routine use of bone marrow smears and cytogenetics is a topic of debate. Currently, in the absence of severe cytopenia, bone marrow cytogenetic analysis is generally not considered predictive of outcomes. Nonetheless, non-i(7q) abnormalities, particularly monosomy 7, are associated with poor outcomes and may progress to advanced MDS or AML, evolving from earlier stages of MDS[22].

Systematic bone marrow cytogenetic examination may play a role in surveillance for patients undergoing long term therapy with granulocyte-colony stimulating factor (G-CSF). In summary, performing bone marrow aspirate and biopsy is recommended at the time of SDS diagnosis, in cases showing changes in complete blood counts (CBC) and annually among patients undergoing G-CSF therapy. For patients with a stable clinical status and normal blood counts (not on G-CSF), routine bone marrow aspirate with cytogenetic examination can be proposed every one to three years.

Treatment

Monitoring and observation

Patients with SDS exhibiting minor hematologic abnormalities without requiring blood or platelet transfusions are closely monitored. A CBC is recommended every three to four months and a bone marrow examination is performed annually to observe blood cell characteristics. This monitoring aims to detect the onset of MDS and AML.

Treatment of hematologic and infectious complications

Cytokine therapy such as granulocyte colony-stimulating factor (G-CSF) and broad-spectrum antibiotics are needed for those with febrile neutropenia. However, caution is advised due to the increased risk of cancer among patients with SDS as mentioned above. Most individuals with SDS typically do not require G-CSF due to the low incidence of infections. However, for those experiencing recurrent invasive bacterial or fungal infections alongside severe neutropenia, chronic use of G-CSF may be considered. Administering G-CSF for profound and persistent neutropenia has shown effectiveness in inducing a clinically beneficial neutrophil response. Patients might respond well to an intermittent schedule with low doses of G-CSF (2 to 3 μg/kg every 3 days) or, in some cases, may require continuous higher doses.[18] The primary goal of long-term G-CSF treatment is unnecessary to achieve normal hematologic parameters but rather to prevent infections. In instances of G-CSF resistance, particularly when associated with severe infections, hematopoietic stem cell transplantation (HSCT) should be considered. Hormone therapy with erythropoietin has shown limited efficacy in increasing hemoglobin levels among these patients. Androgen therapy may provide only temporary benefits and is less effective compared with results from patients with FA. Given the common liver abnormalities in SDS, the side effects of androgen therapy may be more pronounced than those among patients with FA.[18] Androgens enhance hematopoiesis through at least two mechanisms. Firstly, they increase red blood cell mass by stimulating the production of erythroid progenitors in the bone marrow. This is achieved either by boosting erythropoietin (EPO) production in the kidneys or by directly activating the EPO receptor on progenitor cells.[23] Secondly, androgens

Table 2. Recommended treatment options

Treatment Option	Recommendation
Infectious prophylaxis	G-CSF[18,21] (2 to 3 μg/kg every 3 days)
Hormone therapy	Androgen therapy[23,24,26] (A variety of androgen formulations have been used)
Pancreatic insufficiency management	Pancreatic enzyme replacement[5,18] - Initial dose is 2,000 lipase units/Kg body weight/day - Maximum dose is 10,000 lipase units/Kg body weight/day
Hematopoietic Stem Cell Transplantation	The criteria for considering patients for HSCT[18] - Severe cytopenia (hemoglobin less than 7 g/L, absolute neutrophil count less than 500 cells/μL with recurrent infections, platelet count less than 20,000/μL) - MDS with excess blasts - Overt leukemia

elevate telomerase (TERT) gene expression in hematopoietic cells. This effect is mediated by the conversion of androgens into estrogen. The TERT promoter region contains estrogen receptor elements, and exposure to androgens or estrogens increases TERT mRNA levels in hematopoietic cells. This stimulation is blocked by aromatase inhibitors, preventing the conversion of androgens into estrogens.[24] In a mouse model of aplastic anemia, testosterone therapy upregulated telomerase expression, increased peripheral blood counts and elongated telomeres in peripheral blood leukocytes over time.[25,26] Conversely, sex hormone treatment did not produce the same results in telomerase-deficient mice, indicating that the effects of androgens on telomeres and hematopoiesis are mediated by telomerase. Supporting these findings, a large epidemiological study of 980 men found that serum dihydrotestosterone and estradiol levels were positively correlated with age-adjusted telomere length, and functional aromatase polymorphisms were associated with lower estradiol levels and shorter telomeres.[25] This further implicates this pathway in the regulation of telomere length among humans. Additionally, danazol treatment has been shown to elongate telomeres among humans with telomeropathies. Finally, androgens improve hematopoiesis by stimulating other cellular pathways in hematopoietic stem and progenitor cells or by affecting the marrow microenvironment.[25]

PI management is addressed by enzyme replacement therapy using pancreatic enzymes and fat-soluble vitamin supplementation. Tailoring the treatment approach based on the specific hematologic abnormalities and clinical manifestations of each patient is crucial. Additionally, regular follow-up and close monitoring are essential to manage complications effectively.[18]

Hematopoietic Stem Cell Transplantation Currently, HSCT is considered the standard treatment to address hematologic issues among patients with SDS.[27,28]

The criteria for considering patients for HSCT[18] (related or alternative) include the following parameters.

(a) Severe cytopenia (hemoglobin less than 7 g/L, absolute neutrophil count less than 500 cells/μL with recurrent infections, platelet count less than 20,000/μL)
(b) MDS with excess blasts
(c) Overt leukemia

Summary

The survival rate for patients with SDS after receiving HSCT is reported at 64.5% at 1.1 years posttransplant. Causes of mortality include side effects of the conditioning regimen, poor engraftment, veno-occlusive disease, pulmonary disease and graft-versus-host disease caused by the donor's cells reacting against the patient's cells. Carefully assessing the eligibility for HSCT based on specific criteria and considering potential complications that may arise during and after the transplantation process is essential. Close monitoring and prompt management of complications are crucial for improving the overall outcome of HSCT among patients with SDS.

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