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Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

*Original Citation:*

Infections in multiple myeloma / F. Paradisi; G. Corti; R. Cinelli. - In: INFECTIOUS DISEASE CLINICS OF NORTH AMERICA. - ISSN 0891-5520. - STAMPA. - 15:(2001), pp. 373-384.

*Availability:*

This version is available at: 2158/329787 since:

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## INFECTIONS IN MULTIPLE MYELOMA

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### INTRODUCTION

Multiple myeloma (MM) is a plasma cell neoplasm resulting from proliferation of immunoglobulin-secreting cells derived from B-cells (memory B-cells, plasmablasts, plasma cells). MM belongs to the group of monoclonal gammopathies (MGs), in that a monoclonal protein (mostly, an immunoglobulin G (IgG) is present in the serum or urine of almost all patients. In large series of patients with a serum monoclonal protein, IgG accounted for 61%, IgM for 18%, IgA for 11%, IgD for 0.5%, whereas 6% of the subjects had only a monoclonal light chain.<sup>19</sup> The spectrum of MGs ranges from asymptomatic conditions (MG of unknown significance) to active MM.

Strong evidence for the existence of myeloma has been found in Egyptian mummies; however, adequate studies were initiated in the mid 19th century: Macintyre published the first case report in 1850 in England,<sup>20</sup> and at the same time Bence Jones characterized the urinary light chains of a patient with myeloma,<sup>4</sup> whereas in 1873 Rustitzky first used the term "MM."<sup>21</sup>

MM causes approximately 1% of all malignant disorders and 10% of all hematologic malignancies in US whites, whereas figures of 2% and 30%, respectively, are observed in African-Americans.<sup>33</sup> Its incidence

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INFECTIOUS DISEASE CLINICS OF NORTH AMERICA

VOLUME 15 • NUMBER 2 • JUNE 2001

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increases with age, being uncommon before 40 years of age and exceedingly infrequent before 30; survival in young patients (4–5 years) seems to be longer than that observed in all age groups (2–3 years), disease progression and infections being the main causes of death.<sup>6</sup> Risk factors for MM have been studied extensively in the past, and ionizing radiation appears to be the only established one, as results from analyses in atomic bomb survivors and radiologists. Other possible risk factors follow:

- Occupational exposures in farming, agriculture, and industries (asbestos, plastics, pesticides, petrochemical products, rubber)
- Drugs: antibiotics (chloramphenicol, erythromycin, gentamicin, sulfamethoxazole), antiepileptics (diazepam, phenobarbital) + ibuprofen, propranolol, propoxyphene, laxatives
- Family history of MM and autoimmune diseases
- Genetic abnormalities (14q + translocation, 13q monosomy)
- Pre-existing medical conditions: allergies, diabetes mellitus, medical implants, rheumatoid arthritis, chronic infections (malaria, tuberculosis)

However, the strength of the association of these factors with MM is generally either moderate or weak. It also has been suggested that MM could represent an uncontrolled or abnormal immune response to chronic antigenic stimulation, like that of several common autoimmune, chronic diseases and chronic bacterial or viral diseases. However, no associations have emerged with any of the common childhood viral illnesses, while, with regard to bacterial infections, scarlet fever is shown to be associated with significant elevation in risk; people reporting a past diagnosis of pulmonary tuberculosis, pyelonephritis, or malaria have an elevation in risk.<sup>16</sup>

As far as the etiology of MM is concerned, recent evidence of chromosomal abnormalities has been found in most, if not all, MM patients: a major translocation involves the heavy chain Ig gene locus on the long arm of chromosome 14. Other important news takes into account the role of the human herpesvirus-8 (HHV-8), possibly through the expression of interleukin-6 (IL-6): DNA sequences of HHV-8 have been found in nonmalignant bone marrow dendritic cells and in the peripheral blood of most MM patients.<sup>5</sup>

A better understanding of the pathogenesis of MM produces major advances in treatment; thus, interferon alpha can be useful as it has a strong inhibitory effect on IL-6 mediated myeloma cell growth,<sup>23</sup> and dexamethasone causes myeloma cell apoptosis by downregulating IL-6 and IL-6 receptor gene expression.<sup>17</sup> Although oral combination treatment with melphalan and prednisone is still standard, new therapeutic approaches have been tried as the survival of patients remains unsatisfactory. So, a number of combinations of melphalan with Adriamycin, carmustine, cyclophosphamide, doxorubicin, vincristine, dexamethasone, and prednisone have been employed, and either autologous or

allogenic bone marrow transplantation (BMT) or autologous stem cell transplantation (SCT).<sup>36</sup>

Both alkylant/steroid therapy and BMT/SCT produce major suppression of the immune system, which is added to the mild neutropenia and, primarily, to the marked depression in production of normal immunoglobulins typically seen in most MM patients. All of the above can sufficiently explain why—besides the clinical picture generally including bone pain, pathologic fractures, fatigue and weakness, anemia, hypercalcemia, and renal failure—recurrent infections are an important cause of morbidity and the most common cause of death in these patients.

#### IMMUNITY AND MULTIPLE MYELOMA

Patients with MM have serious abnormalities of humoral immunity, consisting in impaired antibody formation after antigenic stimulation and depressed polyclonal (nonparaprotein) immunoglobulin levels in serum. A number of hypotheses have been proposed to explain the humoral immune deficiency associated with MM. Theories ascribing decreased polyclonal serum immunoglobulin levels to a feedback inhibition by the elevated monoclonal immunoglobulin level are not well-founded, as this reduction also occurs in patients whose malignant plasma cells do not secrete paraprotein. Theories attributing humoral immune impairment to plasma-cell tumor-induced depletion of the essential nutrients or myelophthisic expansion also are unsatisfactory; indeed, the immune deficiency seen in MM far exceeds the minor humoral immune impairment observed with most other tumors of comparable total body burden, including other neoplasms beginning in the bone marrow. Instead, two other theories explaining the impaired B-lymphocyte function are of interest: the first one postulates that myeloma tumor cells release infective subunits of ribonucleic acid (RNA) that alter the expression of normal immunoglobulin receptors on the surface of host B lymphocytes, impairing foreign antigen recognition and antibody formation. The second one postulates that myeloma tumor cells release specific mitotic inhibitors (called "chalones"), that block the critical expansion of normal B-lymphocyte clones in response to antigenic challenge. Another interesting theory provides an explanation focused on the potential importance of host immunoregulatory cells. In fact, peripheral blood lymphocytes from patients with MM profoundly depress polyclonal immunoglobulin production *in vitro*. Some patients have circulating mononuclear cells that suppress the immunoglobulin synthesis of normal lymphocytes in coculture, so that one mechanism for the humoral immunodeficiency seen in MM patients is an inhibition of B-cell function by host suppressor cells. Purified T-cells do not mediate the suppressive effect *in vitro*; on the other hand, depletion of phagocytic mononuclear cells nullifies suppressor activity, providing some evidence that the suppressor cell in some patients with MM is a monocyte.<sup>7</sup>

Cellular immune defects also have been described in patients with

MM, particularly, neutrophil function seems to be depressed in proportion to the paraprotein level and disease activity.<sup>24</sup>

#### INFECTIONS AND MULTIPLE MYELOMA

Infections are a major cause of morbidity in patients with MM, are often life-threatening problems and have a multifactorial origin. On the one hand, there are factors deriving from B-cells and their function, such as the decreased levels of circulating immunoglobulins (no paraprotein), the worsened response in producing immunoglobulins, and the delay in IgM synthesis; on the other, there is the depression in the function of the reticuloendothelial system and a decreased migration of neutrophil granulocytes.<sup>37</sup>

Reported frequency of infections in MM patients varies from 1.29 to 2.22 episodes per patient-year. The susceptibility to infections varies with the phase of illness, and disease progression can be divided into several phases. All newly diagnosed patients are designated as being in an induction phase; the plateau phase is defined as minimal disease symptoms or asymptomatic patients with stable paraprotein and  $\beta_2$ -microglobulin levels for greater than 3 months; patients neither in induction nor plateau phases are defined either as relapsers if receiving chemotherapy for recurrence of symptoms or as having progressive disease.<sup>18</sup> The first 2 months of initial chemotherapy are a particularly high-risk period for infections. During this time, almost half of the patients experience at least one clinically significant infection, so that the incidence becomes 4.68 infections per patient-year. After the first 2 months of therapy, infection risk declines to 1.04 infections per patient-year and the rate of infection during the following months is independent of infections acquired in the first 2 months. These early infections are severe, with almost one third of them proving to be fatal and many others leading to substantial delays and dose reduction in administering chemotherapy causing substantial morbidity for patients. Indeed, those with an objective response to chemotherapy undergoing remission of MM have an incidence of infections of 0.44 episode per patient-year, even though chemotherapy is continued until relapse.

There is an association between pretreatment risk factors and the incidence of infections during the first 2 months of chemotherapy: serum creatinine levels at 2 mg/dL or more and deficiency of polyclonal immunoglobulins are significant adverse risk factors, although a trend toward increased infection risk has been noted in patients with advanced age, clinical stage III disease, light chain myelomas and secretion of lambda light chains.<sup>15</sup> Pretreatment leukopenia is not associated with an increased incidence of infection. Some series report that up to 35% of patients die because of early infections and the death rate per infection is 23%. There are many possible explanations for this increased infection risk during the first 2 months of initial chemotherapy: the first cycle of chemotherapy is usually administered at full doses, whereas drug dos-

age in subsequent cycles is adjusted in presence of cytopenias. Patients with hypercalcemia receive mithramycin or corticosteroids before starting chemotherapy for MM and, finally, some myelotoxicity from alkylating agents is usually evident by 7 to 10 days, whereas evidence of tumor response with improved bone marrow function may not occur for weeks. Patients surviving an episode of early infection are not at increased risk of late infections. Standard chemotherapy of MM relieves bone pain, improves mobility, causes objective regression of tumor mass and prolonged survival in most patients, so that there is a need for close observation during the first 2 months of chemotherapy to recognize and treat infections promptly.<sup>21, 22</sup>

Infections are the main cause of death in most patients with hematologic malignancies; bacterial infection accounts for 43% of mortality, fungal infections for 28%, viral infections for 9%, mycobacterial infections for 7%, and polymicrobial infections for 11%. The impairment of host defenses is the main factor responsible for these events. Other environmental factors are hospital air pollution, lack of hygiene by the staff in handling patients, and uncooked food. Among iatrogenic factors, increasing use of indwelling vascular catheters, frequent venipunctures, bladder catheters, and diagnostic and therapeutic invasive procedures are important. Advanced age, malnutrition, bed confinement, and underlying chronic diseases can increase the risk of developing infections.<sup>20</sup>

It is useful to divide infections arising in the compromised patient into three categories: (1) infections resulting from host defects caused by the disease itself; (2) infections based on the host defects induced by disease and worsened by various therapeutic agents; and (3) infections related only to therapeutic agents, surgical procedures, or medical interventions. In MM patients, the increased susceptibility to infections is more related to hypogammaglobulinemia than to granulocytopenia because of opsonin deficiency rather than leukocyte defects.<sup>25</sup>

Most infections occurring in patients with MM involve the urinary and respiratory tracts, with or without the development of sepsis. In many reports, patients with septicemia cannot be distinguished from those without septicemia in respect to age, sex, drug therapy, azotemia and serum calcium levels, or white blood cell count. In septic patients the disease duration is usually longer and hemoglobin values are lower than in nonseptic subjects, but almost all have low levels of IgM and IgA with elevated or low levels of IgG.<sup>27</sup> As far as the etiology of infections is concerned, *Streptococcus pneumoniae* is the organism that classically comes to mind as the causative agent of most infections in MM patients; however, many reports have pointed out that gram-negative bacilli (GNB) are increasing in frequency, especially in hospitalized patients.<sup>28</sup> Since the 1960s, GNB have become more common than *S. pneumoniae* in MM patients; moreover, there has been an increasing incidence in hospital-acquired infections caused by GNB.<sup>13, 27, 28</sup> In many reports, the frequency of GNB infections varies from 70% to 81% in patients with MM, particularly in hospitalized patients, whereas most reported infections caused by *S. pneumoniae* seem to be community

acquired. The incidence of hospital-acquired infections has been reported to increase in MM patients, *Escherichia coli* being the most frequently isolated organism; most bacterial species isolated have origin in the urinary tract. Globally, up to 55% of infections in MM patients are hospital acquired: urinary tract infections, often following insertion of a Foley catheter, are found most frequently, followed by intravenous catheter infections caused by *Staphylococcus epidermidis*. Most patients who die have a hospital-acquired infection.<sup>13</sup> There is a biphasic pattern of bacterial infections in patients with MM: "presenting" episodes, occurring before hospitalization, chemotherapy, or both, and "late" episodes, occurring after hospitalization or therapy.

Among presenting infections, almost all episodes are caused by *S. pneumoniae* or *Haemophilus influenzae*. After presentation, *S. pneumoniae*, *H. influenzae*, and other streptococci occur in the first 8 months of disease whereas GNB and *Staphylococcus aureus* cause almost 90% of episodes 8 or more months after diagnosis; of these, 87% are hospital acquired and cause 92% of deaths from infection. In particular, *S. pneumoniae* is the most frequent pathogen in patients whose disease is newly diagnosed and still not unaffected by hospitalization and chemotherapy.

In patients with MM, neutropenia does not appear to be the major factor predisposing to GNB infections, even in patients with sepsis; indeed, almost all gram-negative septic episodes occur in nongranulocytopenic patients.

Disease activity, as reflected in paraprotein levels, is also related to the type of infection; infections caused by gram-positive cocci (GPC) occur mainly in patients with untreated, active disease, or in patients responding to administered chemotherapy, whereas GNB episodes occur primarily in subjects with advanced or refractory disease. In patients responding to therapy, GNB infections are rare in absence of neutropenia.

Recurrent episodes of pneumococcal infection are known to occur occasionally in patients with profound immune defects; the recurrent infection may present after a short symptom-free interval and may be caused by the same bacteria (relapse) or by different pathogens belonging to the same or different species, usually after a long symptom-free period (recurrence). Some reports show that the presence of MM is a clear predictor of recurrence, and recurrence is more than an anecdotal risk in MM patients with bacteremic infections caused by *S. pneumoniae* (reported prevalence of 2.8%). There is a high mortality rate associated with recurrent episodes (47%), and the mortality rate during the first episode is high, varying from 5% to 43%.<sup>34</sup>

Pneumonia is present in 79% of bacteremic episodes. Pneumococcal serotypes identified include 23F, 14, 4, 1, 6A, 3, 5, 6B, 7F, 9N, 9V, 12F, 13, 17F, 18C, 19F, and 37; however, on clinical grounds a number of isolates are not susceptible to penicillin (MIC  $\geq 0.1$  mg/L) and other beta-lactam or non-beta-lactam agents.<sup>9</sup>

Increasing worldwide resistance of *S. pneumoniae* to penicillin has been attributed to acquisition of foreign genetic material by transforma-

tion or mutations in genes coding for penicillin-binding proteins, processes that may be promoted by selective pressure of antibiotics. In North America, penicillin-resistant pneumococci are now found in almost all medical centers, their prevalence varying among different regions, time period, and site of isolation. In the 1980s the prevalence of penicillin-intermediate pneumococci (MIC = 0.1–1 mg/L) was only 4%. In the 1990s, there was a dramatic increase in penicillin resistance among pneumococci from medical centers throughout the United States: only 78% of strains were susceptible to penicillin, whereas 7% were fully resistant (MIC > 1 mg/L),<sup>2</sup> Doern et al have found a prevalence of 23.6% of non-susceptible pneumococcal strains, with 14.1% intermediate and 9.5% high-level resistant in 1994–95; the same authors have found a prevalence of 27.8% and 16%, respectively, for penicillin-intermediate and penicillin-resistant pneumococcal strains isolated from the respiratory tract in 1997 in the United States; in Canada these values were 21.8% and 8.4%, respectively.<sup>10, 11</sup> The United States is divided into nine regions established by the United States Census Bureau: Pacific, Mountain, West North Central, East North Central, New England, Mid-Atlantic, South Atlantic, East South Central and West South Central. Penicillin resistance is highest in the South Atlantic (44%) and East South Central (43%), regions, whereas it is lowest in the New England (28%) and Mid-Atlantic (28%) regions.<sup>11</sup>

The Alexander Project was established in 1992 to examine antimicrobial susceptibilities of bacterial isolates from community-acquired infections of the lower respiratory tract. Europe, France and Spain have been established as areas with high rates of *S. pneumoniae* penicillin resistance, with combined numbers of intermediate and resistant strains now accounting for some 50% of isolates. The United States has an increase in the prevalence of both intermediate and highly resistant isolates (12.7% to 15.3% and 16.6% to 18.6%, respectively). In Central and South America, high rates of penicillin-resistant strains have been seen in Mexico.<sup>14</sup>

Resistance to penicillin frequently signals resistance to other antimicrobial agents, including other penicillins, cephalosporins, macrolides, lincosamides, tetracycline, and cotrimoxazole. Macrolide resistance exists primarily in one of two forms: strains with altered ribosomal targets caused by expression of the *ermAM* gene and active efflux pump caused by expression of the *meffE* gene.<sup>12</sup> Overall rates of macrolide resistance for isolates collected in 1996 and 1997 were 16.5% and 21.9%, respectively. High resistance rates have been found for doxycycline (21.8% in 1997), with the highest prevalence in Hong Kong, Poland, Spain, France, Italy, Belgium, Hungary, Mexico, Saudi Arabia, South Africa, and the United States. Resistance to cotrimoxazole is generally widespread.<sup>14</sup>

Antibiotic therapy targeted to pneumococcal infection must take resistance issues into account. Infections caused by strains fully still susceptible to penicillin can be effectively treated with penicillin G. In patients with infection caused by intermediately resistant strains, high-dose penicillin G can be used in pneumonia, whereas a third-generation cephalosporin is preferred for meningitis and bacteraemia. Lastly, either

a broad-spectrum beta-lactam (cefepime, imipenem, meropenem) or the combination of vancomycin with a third-generation cephalosporin is the therapy of choice for infections caused by fully resistant strains.<sup>20</sup> The latter combination also seems to be advisable in suspected pneumococcal infection pending the results of culture and antimicrobial susceptibility testing.

The lung can be identified as the primary site of pneumococcal infection in up to 75% of cases; nonpulmonary sources mainly consist of the central nervous system and pharynx, whereas up to 32% of bacteremias have no identifiable source of the infection. Mortality rate is 100% in patients inadequately treated.<sup>8</sup>

Recurrent pneumococcal infections, especially pneumonia, can be the presenting feature of MM, so that such a diagnosis warrants investigation for underlying myeloma.<sup>1</sup> Such data indicate that patients with MM and bacteremic pneumococcal infection should be offered antipneumococcal vaccine despite doubts about their efficacy; indeed, serum levels of IgG2 subclass, which is the class of immunoglobulins used for the response to capsulated antigens, are universally reduced in MM patients.<sup>18</sup>

The other important agent of community-acquired infections in MM patients (i.e., *H. influenzae*), also has resistance issues. Ampicillin resistance mediated by the production of beta-lactamases currently is frequent in some countries. Based on the results of the Alexander Project, incidence rates of beta-lactamase-positive strains have reached 20% to 40% in Europe (Belgium, France, Spain), America (United States, Mexico), and Asia (Saudi Arabia, Hong Kong).<sup>14</sup> A national antimicrobial resistance surveillance study conducted in 1997–1998 in the United States evidenced a 33% percentage of beta-lactamase-producing *H. influenzae* strains.<sup>41</sup> Because of this epidemiologic pattern, documented or suspected *H. influenzae* infections should be preferentially treated with beta-lactamase-resistant beta-lactams (i.e., "protected" aminopenicillins, amoxicillin-clavulanate, ampicillin-sulbactam) or third-generation cephalosporins.

There has been no decline in the frequency of GPC infections in MM patients, whereas the number of hospital-acquired GNB episodes has risen sharply since the early 1960s. This increasing frequency may have some explanations: (1) serum bactericidal activity against GNB involving both complement and IgM and IgA levels is low in almost all MM patients; (2) many patients receive corticosteroids or cytotoxic therapy, both of which increase the risk of infections; (3) with the advent of chemotherapy, patients with MM live longer and, therefore, they are hospitalized more frequently, allowing them to acquire a nosocomial infection caused by GPC<sup>20</sup>; and (4) despite administration of chemotherapy, patients with MM can have vertebral collapse and neurogenic bladder that predispose them to urinary tract infections caused by resistant GNB.<sup>42</sup>

Intensive chemotherapy with hematopoietic SCT is increasingly used in treating several malignancies; autologous peripheral blood pro-

genitor cells are now the main source for hematopoietic rescue, as they allow a more rapid hematopoietic reconstitution than bone marrow does. Infections complicating such procedures are the major cause of morbidity and mortality in patients undergoing SCT, although such patients have lower rates of infections than those receiving autologous BMT.

Also during these procedures, we can distinguish early and late infectious complications; following autologous SCT, 30% of patients have an infection within the first 30 days. Among early infections, bacteremias are the most common ones, accounting for more than two thirds (69%) of those events. GPC account for more than 80% of all cases and GNB for 19%. Streptococci are the most frequent GPC, with viridans streptococci often causing the patient's death. Among late infections, unrelated to engraftment failure, varicella-zoster virus infection is the most frequent, accounting for 15% of cases; most patients develop infection within 12 months after transplantation.<sup>21</sup>

Susceptibility to *Neisseria* infections is increased in many complement-deficiency states; acquired complement deficiency associated with meningococemia has been reported in patients with MM, and different syndromes of complement depletion in B-cell proliferation have been described, although their incidence has not been well established.<sup>22</sup> *Neisseria meningitidis* is a rare cause of primary septic arthritis and infection in patients with known MM despite the increased susceptibility to encapsulated organisms, although cases of primary meningococcal arthritis are described in literature.<sup>23</sup>

*Atciliogenes xylosoxidans* subsp. *xylosoxidans* is a nonfermenting peritrichous GNB that is considered an opportunistic pathogen and can be found in aqueous environment. Systemic infections are severe and often lethal despite an optimal therapy not yet well established. Nosocomial infections caused by such pathogens are becoming more important in high-risk patients such as those in hematologic wards, particularly after cytotoxic chemotherapy. Although the source of infection often remains unknown, infection seems to originate from contaminated solutions, as *A. xylosoxidans* can adhere to plastic materials of catheter systems used to administer chemotherapy. Only neutropenic patients develop bacteremia, whereas nonneutropenic patients may develop it a fortnight later. Carbapenems and other antipseudomonal beta-lactams (ureidopenicillins, ceftazidime) can be used for therapy of these infections, but they are unable to eradicate organism persistence on the plastic surface of catheters.<sup>22</sup>

*Chlamydia trachomatis* pneumonia is a rare event in adults, even in immunocompromised hosts, but Vlasveld and Van den Broek have reported one case in a patient with MM.<sup>24</sup> Non-O:1 *Vibrio cholerae* is often associated with extraintestinal infections and has been identified in blood, wounds, sputum, cerebrospinal fluid, peritoneal fluid, and other sites. Bacteremia caused by non-O:1 *V. cholerae* rarely is reported but can occur in patients with underlying chronic conditions that compromise host immunity, particularly hematologic malignant conditions. A combination of intestinal IgA plus exudation of vibriocidal and antitoxin IgG

mediates the destruction of *V. cholerae* locally by hindering motility or attachment; impaired antibody production present in almost all MM patients can explain the emergence of bacteremia caused by such pathogen as described by Shelton et al.<sup>40</sup> Lortholary et al reported the occurrence of invasive aspergillosis in nonallografted patients with MM treated at hematologic or oncology centers in Europe. Most cases occurred in patients with stage III MM and the remainder in patients with stage II MM. The median time between diagnosis of MM and of invasive aspergillosis was 8 months; almost half of the patients had a neutrophil count less than 500/mm<sup>3</sup> for a median duration of 19 days. Most patients had primary pulmonary aspergillosis, the remainder having primary sinus involvement. Invasive aspergillosis occurred as a potentially lethal opportunistic infection in intensively treated nonallografted patients with MM and recent postmortem data report that it is a leading cause of death in patients with MM receiving high doses of treatment. Invasive aspergillosis is always fatal if undiagnosed and untreated.<sup>21</sup>

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