

REVIEW

Exacerbations of severe asthma

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Summary

Exacerbations occur frequently in severe asthma. They result in significant morbidity and can lead to hospitalization and death. Severe exacerbations can also lead to an accelerated decline in lung function. Phenotyping severe asthma can aid with both prognostication of exacerbation risk and maintenance treatment selection to minimize future risks of exacerbations in severe asthma. The rate of exacerbations differs by phenotype, and is most frequent in refractory eosinophilic asthma and early onset allergic asthma. Phenotype specific therapy can reduce exacerbations in both these forms of severe asthma. Exacerbations are multi-component events. Each exacerbation represents an opportunity to assess and target treatment to the domains of airway pharmacotherapy, self-management behaviour, risk factors, and relevant co-morbidities.

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Introduction

Exacerbations of severe asthma are responsible for a large disease and cost burden [1]. People with severe asthma experience poor quality of life and an increased risk of severe exacerbations, permanent loss of lung function, and adverse treatment effects. Management approaches are not strongly evidence-based, and if standard therapy appears to fail then expensive or toxic alternatives are usually trialled. The natural history of asthma includes episodes of acute deterioration, termed 'exacerbations', that occur upon a background of chronic persistent inflammation and/or structural changes. Exposure to certain trigger factors interacts with the underlying pattern and intensity of airway inflammation, the degree of airway hyperresponsiveness and of airflow obstruction, to cause wide variability in the clinical expression of asthma exacerbations. In severe asthma, there are additional factors such as co-morbidities and treatment refractoriness that also influence exacerbation events.

Exacerbations are common in severe asthma. In the United Kingdom, it was found that patients with treatment refractory asthma required a median of four rescue corticosteroid courses in the past year, and that at least 25% required hospital admission for asthma [2]. Similarly, in the USA, the Severe Asthma Research

Programme (SARP) found that in the previous year, 40% of patients with severe asthma required an emergency department visit, compared to 20% in moderate asthma and 15% in mild asthma [3].

The perceived significance of exacerbations tends to be minimized by both patients and clinicians [4, 5]. Consequently, we need to change the perception of exacerbations as a temporary inconvenience, and recognize that asthma exacerbations can be associated with permanent airway damage and a worse prognosis. It is recommended that an exacerbation of severe asthma, or an 'asthmatic lung attack', should prompt a full review of all aspects of the problem, including co-morbidities, management, self-management skills such as adherence, and relevant trigger factors and psychosocial issues [4, 6].

Definitions and terminology

Expert-based guidelines have recently reviewed and updated definitions of severe asthma and of asthma exacerbations.

Severe asthma

Severe asthma is now the recommended term to describe this overall group of disorders, replacing formerly used terms such as difficult asthma, difficult-to-control

asthma, brittle asthma, and refractory asthma. The World Health Organization consultation on severe asthma has developed a uniform definition for severe asthma [7], and defines it as: '*Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children).*'

This global definition includes three subgroups of severe asthma:

- **Untreated severe asthma:** This is a large problem in areas where current therapies for asthma are not widely available [e.g. developing countries], or where access to therapy is limited [some socioeconomic groups in developed countries]. Most patients with this type of severe asthma are considered undertreated, and it is expected that enabling access to asthma controller therapy [inhaled corticosteroid and long-acting beta-agonists] would significantly reduce exacerbations.
- **Difficult-to-treat asthma:** These patients present with uncontrolled asthma despite access to inhaled controller therapy. They have an increased exacerbation risk because of poor management skills (inadequate inhaler technique, non-adherence, no exacerbation management plan) or exposure to trigger factors (allergen, occupational sensitizers, drugs, tobacco smoke). They may also have significant co-morbid conditions such as sinonasal disease, obesity, sleep apnea, gastro-oesophageal reflux disease, vocal cord dysfunction, anxiety, depression, and dysfunctional breathing. These co-morbidities are associated with increased risk of asthma exacerbations, which may be due to an interaction of the co-morbidity and asthma, or symptom misattribution [8]. Patients with difficult-to-treat severe asthma may achieve symptom control by systematically addressing self-management skills, triggers, and co-morbidity [9–11]. It is expected that this systematic approach would reduce exacerbation risk, but this remains to be documented.
- **Treatment resistant severe asthma:** is defined as asthma for which control is not achieved despite the highest level of recommended treatment, and asthma for which control can be maintained only with the highest level of recommended treatment, which is inhaled high dose corticosteroid and second controller therapy. The manifestations of uncontrolled asthma in this setting are poor symptom control, frequent exacerbations [exacerbation prone asthma], and/or very severe exacerbations [brittle asthma], or incompletely reversible airflow obstruction [chronic obstructive pulmonary disease, or overlap asthma-COPD].

These definitions present the concepts that severe asthma is characterized by lack of clinical control, and that exacerbations are both a feature of uncontrolled severe asthma, and a future risk associated with severe asthma.

Asthma exacerbation: definition

An American Thoracic Society/European Respiratory Society (ERS) Task force recently reviewed the extensive literature on the definition of asthma exacerbations [12], and recommended that severe asthma exacerbations be defined as 'events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma'. Exacerbations were further graded into severe and moderate, whereas mild exacerbations were not considered a useful term. The Task Force recommended definition of a severe asthma exacerbation for clinical trials is at least one of the following:

- Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days.
- A hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids [12].

The Task force defined moderate asthma exacerbations as 'events that are troublesome to the patient, and that prompt a need for a change in treatment, but that are not severe'. Moderate exacerbations are clinically identified by being:

- outside the patient's usual range of day-to-day asthma variation, and
- a deterioration in symptoms, lung function, and/or increased rescue bronchodilator use,
- a duration of 2 days or more, but not be severe enough to warrant systemic corticosteroid use and/or hospitalization.

These definitions give considerable clarity to the concept and recognition of exacerbations in asthma. However, there are several areas for future research in this domain. The applicability of these definitions to patients with severe asthma needs further investigation (Table 1). People with severe asthma have a high degree of day-to-day variability in symptoms, a high symptom burden, they may have a component of non-reversible airflow obstruction, and many use systemic corticosteroid for maintenance therapy. This means that people with severe asthma can potentially exhibit features of a moderate or severe exacerbation on a daily basis. Consequently, the recognition of an exacerbation in severe asthma requires further investigation, and there is an opportunity to develop a validated exacerbation

recognition tool, as has been achieved in COPD research [13]. In addition, there is a need to develop validated criteria for the magnitude and duration of change in symptoms and/or beta2-agonist use that define a severe asthma exacerbation. While this is possible using sophisticated statistical techniques, such as control chart analysis [14, 15], the clinical applicability of these techniques in severe asthma requires evaluation.

Asthma exacerbation: terminology

Exacerbation is currently the preferred term for clinical and scientific use to describe the acute episodic deterioration of asthma. However, this term has several problems. It is not recognized by patients with asthma [5]. When this issue was studied among a group of adults

with asthma, almost half were not familiar with 'exacerbation', and only 12% would use the term themselves. The patients preferred the term 'attack', which was the only specific term spontaneously volunteered by the patients with asthma. Similarly, it is considered that the term exacerbation may inhibit effective management by clinicians [4] and recently, the term 'lung attack' has been recommended for use amongst clinicians [4, 6]. Thus, despite being the currently preferred term for research [12], the word 'exacerbation' may not be that useful for communication between patients and clinicians. This represents a clear health literacy gap that may lead to poor clinical outcomes [16, 17], and signals deeper issues regarding attitudes and beliefs to deteriorations in asthma control in the severe asthma setting. Future work is needed to understand and improve this situation.

Table 1. Future research directions for exacerbations of severe asthma

Recognition
Do the ATS/ERS definitions of exacerbations apply equally well in severe asthma?
What constitutes a significant change in B2 agonist use or symptoms to signal the onset of an exacerbation of severe asthma?
Does a systematic assessment of severe asthma using published protocols lead to reduced exacerbation risk?
Terminology
What are the characteristics and impact of the asthma exacerbation communication gap between patients and clinicians?, i.e. underlying attitudes and beliefs, degree of poor health literacy.
Is the quality of care for patients with severe asthma improved by targeting 'lung attacks'?
Impact of Phenotype
What is the impact of the allergic phenotype on exacerbation rate, pattern and recovery?
Specific phenotypes include: severe asthma with fungal sensitisation; nasal disease, aspirin sensitivity.
What is the mechanism of the increased exacerbation rate in severe eosinophilic asthma?
What are the mechanisms of the interaction between allergy and early onset asthma in leading to adverse prognosis and increased future risk of exacerbation?
What is the impact of non-eosinophilic phenotypes on exacerbation rate, pattern, and recovery?
Pattern of Exacerbations
Does therapy of specific exacerbation phenotypes lead to improved outcomes?
What therapies reduce the future risk of asthma exacerbations?
Management
What are the best ways to detect non-adherence and successfully intervene for people with severe asthma?
What is the efficacy of pharmacotherapy directed at each of the components on inflammation in severe asthma?
Does multi-dimensional assessment and individualized management lead to improved outcomes in asthma exacerbations?

Impact of asthma phenotype

Severe asthma is a heterogeneous condition, and this has led to the use of detailed evaluation of clinical characteristics and biomarkers that can be used to identify asthma subtypes [18]. In particular, there is heterogeneity of the inflammatory response in asthma, both in the stable state [2], and during an exacerbation [19]. Recognized inflammatory phenotypes include allergic asthma, eosinophilic asthma, mixed eosinophilic and neutrophilic asthma, and non-eosinophilic forms of asthma such as neutrophilic asthma and paucigranulocytic asthma [19]. These phenotypes imply differences in underlying mechanisms, and it is likely that this may impact on exacerbation rate. The rate of exacerbations in severe asthma can be estimated from prospective studies, such as cohort studies, or the placebo arm of randomized treatment trials (RCTs). In non-severe asthma, a meta-analysis estimated the rate of exacerbations requiring systemic corticosteroid to be 106 exacerbations per 1000 patients over 6 months [20], or an annualized rate of 0.2 severe exacerbations per patient. The exacerbation rates in severe asthma are higher, and may differ by phenotype. In one meta-analysis of RCTs, patients with severe allergic asthma experienced a rate of asthma exacerbations of 1.4 per year [21] (Fig. 1).

It also needs to be remembered that severe exacerbations also occur in both mild and moderate asthma, and given the much higher prevalence of mild/moderate asthma, these are numerically frequent events. The impact of phenotype in mild/moderate asthma may also be important and requires further evaluation.

There is an unexpectedly high prevalence of sensitization to the *Aspergillus fumigatus* and other filamentous fungi in severe asthma [2], and severe asthma with fungal sensitization has recently been highlighted as a specific phenotype [22], that is responsive to antifungal

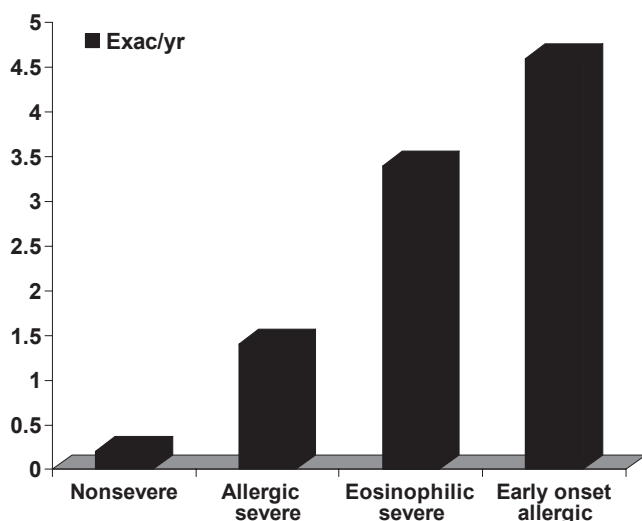


Fig. 1. Impact of asthma phenotype on exacerbation rate.

therapy [23]. This group also experiences a high rate of asthma exacerbation, in one trial 28% of patients had a severe exacerbation.

Treatment refractory eosinophilic asthma seems to have a significantly higher exacerbation rate, with a rate of 3.4 exacerbations per participant reported in one trial [24]. This highlights a potential interaction between airway eosinophilia and exacerbations in severe asthma, which is further strengthened by studies that show a 50% reduction in exacerbation rate when airway eosinophilia is suppressed by either inflammetry guided therapy [25, 26] or specific anti-interleukin 5 therapy [24, 27]. The mechanisms of this interaction are not known. The exacerbation rate in mixed granulocytic asthma (eosinophils and neutrophils) or the non-eosinophilic asthma phenotypes needs to be determined (Table 1).

Another approach to phenotyping severe asthma is to use unbiased methods such as cluster analysis [1, 28, 29]. These approaches identify that severe asthma with airflow obstruction has a higher exacerbation risk [28]. The study by Halder et al. identified four clusters in the severe asthma population [29]. Each of the subtypes reported a high rate of severe exacerbations, with exacerbation rates between 3.4 and 4.6 in the past year. Early onset atopic severe asthma had the highest exacerbation rate (4.6/year), which is consistent with the allergic phenotype of severe asthma discussed above. In both cluster analyses [28, 29], the age of onset of allergic asthma emerged as a significant prognostic factor. For example, the exacerbation rate in severe allergic asthma (age of onset unspecified) is 1.4/year [21], but this increases to 4.6/year for early onset severe allergic asthma [29]. The mechanisms of this age related effect on exacerbation rate is unclear, but may represent an interaction between allergic inflammation

and either airway remodelling or developmental aspects of airway growth.

Similarly, the impact of obesity on asthma is greatest in those with early onset asthma [30]. Obesity is associated with a non-eosinophilic pattern of airway inflammation [29], and with systemic non-allergic inflammation [31, 32]. These processes may interact to augment asthma severity and exacerbation risk.

It is likely that there are differential effects of treatment on exacerbation risk in the different severe asthma phenotypes. If this is the case, then phenotype-guided therapy should yield improved results for severe asthma.

Patterns of exacerbations

Asthma exacerbations follow a definable pattern (Fig. 2) [33] where there is an abrupt and progressive decline in lung function (phase 1), that can vary in both acuity of onset, rate of decline, and extent of decline. This occurs on a background of maintenance asthma (phase 0), that can also vary in stability, extent of variation, and overall level of lung function. The exacerbation can then progress to death, or to recovery (phase 2). Recovery can be rapid, or in some cases, protracted, with a delayed return to baseline (phase 3). These phases are important as they imply different mechanisms that are in operation, and potentially different types of intervention.

Phase 1: Most severe asthma exacerbations leading to hospitalization are associated with respiratory viral infection, most often rhinovirus [34].

There is also evidence of synergy between viral infection and other triggers such as allergen exposure that may be important in atopic adults [35].

Several studies show that people with asthma have a specific immune effect leading to impaired antiviral interferon responses after viral infection [36, 37, 38], and this may lead to more frequent, more severe, and persistent rhinoviral infections [39], as well as an exaggerated airway inflammatory response [40]. This defect is apparent upon challenge by viral infection, and does not appear to influence baseline levels of antiviral

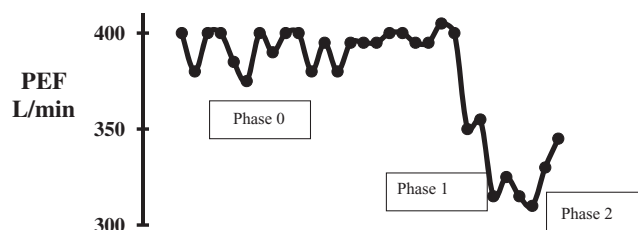


Fig. 2. Pattern of Exacerbations. Mechanisms and potential treatments are different in each phase. Peak expiratory flow (PEF) is peak expiratory flow.

interferon lambda, which are normal in asthmatic airways [41].

Randomized treatment trials consistently demonstrate that inhaled corticosteroids reduce the rate of severe exacerbations in asthma, and also improve eosinophilic inflammation. This implies an effect of eosinophilic inflammation in the mechanistic pathway of severe exacerbations, and also an interaction between eosinophilic inflammation and viral infection as a trigger of severe exacerbations. The precise nature of these effects requires further study. The possibilities include the need for exposure to more than one trigger to result in a severe exacerbation. For example, Green et al. showed an interaction between viral infection, allergen exposure, and atopic sensitization conferred the greatest risk of triggering severe exacerbations [35]. Alternatively, eosinophilic inflammation may adversely impact on epithelial antiviral responses. This could occur by increasing viral receptor expression on epithelial tissue, and thereby increasing susceptibility to viral infection [42].

Alternatively, eosinophilic inflammation may suppress, or inhaled corticosteroids may directly enhance antiviral interferon production, as interferon lambda levels were highest in those asthmatics taking inhaled corticosteroids [41].

Support for this at a clinical level is provided by a secondary analysis of an inflammometry guided asthma RCT [26], where PCR-positive viral infections were found to be reduced when asthmatic women were managed by inflammometry.

There is also evidence that both adaptive IL-10 pathways are enhanced, and signalling by innate immune receptors including TLR-2 and TLR-3 [43].

At present we do not have effective interventions to inhibit rhinoviral infection of the consequent inflammatory responses. Corticosteroids are likely to be ineffective. Immune modulators, such as macrolides, have appeal because of their inhibitory effects on many of the inflammatory pathways that are activated in this setting [44].

Phase 2: once an exacerbation is established, there is evidence of intense inflammation with granulocyte influx of neutrophils and eosinophils [19, 40], granulocyte activation, mucus hypersecretion, airway mucosal oedema and vascular leakage, epithelial desquamation, and airway smooth muscle contraction. Treatment in this phase is well-defined and supported by level one evidence, and includes aerosolised rapid acting bronchodilators, systemic corticosteroids, and maintenance of oxygenation [45]. The pattern of severe exacerbations is considered to generally follow an abrupt deterioration in lung function within hours to days of the exposure to the trigger, as shown in Fig. 2. However, clinicians also recognize a slower and more protracted deterioration, particularly in severe refractory eosino-

philic asthma. The mechanisms of this altered pattern remain to be investigated, and similarly, the existence of other patterns or trigger specific patterns is also in need of further investigation. Fluctuation analysis offers a promising approach to investigate these patterns and their determinants [46].

Phase 3: Recovery usually ensues over several days. However recovery can be delayed, leading to persistence of airflow obstruction [47]. Interestingly, this phenomenon is not restricted to asthma attacks, but can also occur in other obstructive airway diseases such as cystic fibrosis [48]. The mechanisms of delayed recovery are unknown, but do not seem to involve active airway inflammation [47] or persistent viral infection [49]. It is possible that exaggerated healing (fibrosis, remodelling) may lead to delayed recovery of lung function after a severe asthma exacerbation.

Risk factors

A range of well-defined risk factors for asthma exacerbations have been identified and reviewed [18]. The trigger factors for asthma exacerbations each elicit specific inflammatory responses (Table 2). These can influence the inflammatory phenotype observed during an exacerbation, and this information can potentially be used to guide therapy. At present, management of exacerbations is based on severity, however, it is possible that phenotype-guided therapy of exacerbations may be superior.

Future risks of exacerbations

Severe asthma exacerbations have longer term consequences. These include more exacerbations [50], and an accelerated decline in lung function [51] [52]. In a prospective observational study, Bai et al. found that one exacerbation per year leads to a 30 mL greater decline in FEV₁ [51]. Interestingly, both future exacerbation risk and loss of lung function may be modified by optimal asthma therapy with inhaled corticosteroid. A posthoc analysis of the START study, found that the accelerated decline in lung function in adults who had a severe exacerbation was reduced in those on budesonide [52].

Management

To reduce the frequency and severity of exacerbations in severe asthma, management and follow-up requires greater attention. Severe asthma is a heterogeneous condition in terms of its pathophysiology, associated co-morbidities, and significant social and psychological impacts. These factors lead to high exacerbation rates. Consequently, a different management approach is

Table 2. Airway inflammatory response to triggers of asthma exacerbations

Eosinophilic
Allergen
Fungal allergens
Occupational sensitizers
Corticosteroid reduction
Psychological factors: stress
Aspirin
Premenstrual asthma
Chronic sinusitis
Neutrophilic
Virus infection
Bacterial infections, including Chlamydia
Tobacco smoke
Occupational exposures
Obesity
Mixed eosinophil/neutrophil
Virus infection
Fungal allergens
Bacterial infection
Occupational exposures
Unknown
Gastro-oesophageal reflux
Genetic factors

Adapted from Hargreave and Nair [59].

needed that addresses these issues. Understanding and managing the heterogeneity in severe asthma is now recognized as the major challenge for this disease [53]. One option is multi-dimensional assessment and intervention. This approach, also termed as 'care bundles', is similar to those used in cardiology for myocardial infarction ('heart attacks') [4], the management of elderly people with co-morbidities [54], and the management of complex airway diseases such as asthma in elderly people [55]. For severe asthma, assessment and intervention domains need to focus on several key components (Fig. 3):

- Behavioural: the optimization of asthma management skills through education programmes that include prescription and translation of written asthma action plans,
- Risk factors: the reduction of risk factors with interventions such as intensive smoking cessation, weight management programmes, and effective management of triggers,
- Airway: optimal pharmacotherapy,
- Co-morbidity: management using guideline based care.

Asthma management skills in this population are poor. In one study, only 34% of severe asthma patients who were managed in tertiary care recalled being prescribed a written asthma action plan [11]. Treatment adherence is also poor in this population [56]. A prospective study found that 24% of severe exacerbations

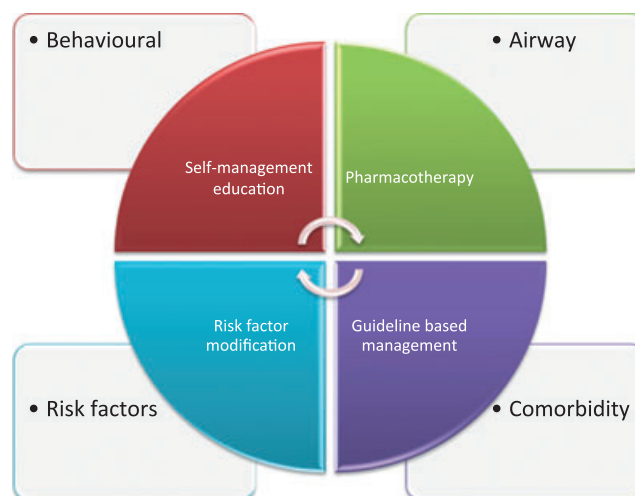


Fig. 3. Components of exacerbations in severe asthma and treatment interventions adapted from Gibson, McDonald and Marks [55].

were attributable to non-adherence [57]. The best ways to detect non-adherence and successfully intervene for people with severe asthma need to be defined. Co-morbidities that complicate and exacerbate severe asthma are common [8, 11]; these factors are rarely addressed during the three exacerbation phases, but should be. Optimal pharmacotherapy for asthma exacerbations is at present based on treating bronchospasm with aerosol bronchodilators, supportive oxygenation where required, and corticosteroids [45]. Systemic corticosteroids target some parts of the inflammatory response, such as eosinophilic inflammation, airway oedema and vascular leakage, and possibly mucus secretion. New opportunities for treatment of severe exacerbations include targeting airway inflammation more specifically and/or more effectively, directly targeting trigger factors, or using immunomodulatory therapy.

This approach of multi-dimensional assessment (MDA) and individualized management (IM) has been designed for asthma [55], adapted to severe asthma [11], and tested in older people with asthma and COPD where it was found to be effective. Management using MDAIM resulted in major improvements in both health [quality of life] and biological outcomes [58]. Following systematic assessment of the components of a severe asthma exacerbation (Fig. 3), an individualized treatment programme is developed with the patient that targets their clinical problems. The treatment programme applies a phenotype based approach and links biomarkers with case management. MDAIM involves individualized problem-based management that is person-centred, evidence-based, co-ordinated with each aspect of care. This approach can be initiated during any of the exacerbation phases (Fig. 2).

Conclusion

Exacerbations, are a common problem in severe asthma. They are multi-component events that are associated with an increased risk of future exacerbations and accelerated decline in lung function. Research is needed to better define the recognition, mechanisms, and management of severe asthma exacerbations. Current clinical care can be optimized by addressing airway pharmacotherapy, self-management skills, triggers and risk factors, and co-morbid diseases that impact on the outcome of severe asthma.

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