Scientific Research Publishing

International Journal of Clinical Medicine, 2022, 13, 571-583
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Probiotics for Antibiotic-Associated Diarrhea: What, When, and How Long?

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How to cite this paper: Ferguson, J.R. and Taylor, K. (2022) Probiotics for Antibiotic-Associated Diarrhea: What, When, and How Long? *International Journal of Clinical Medicine*, **13**, 571-583.
https://doi.org/10.4236/ijcm.2022.1312043

Received: November 8, 2022
Accepted: December 3, 2022
Published: December 6, 2022

Abstract

Probiotics have been formally defined as "live microorganisms that confer a health benefit on the host when administered in adequate amounts." Although a range of applications has been explored for probiotics, their utility in antibiotic-associated diarrhea (AAD) is both biologically plausible and supported by abundant clinical evidence. However, the strength of evidence underlying the efficacy of specific strains and formulations for AAD varies widely. This review leverages recent meta-analyses and systematic reviews to clarify some outstanding issues on the utility of probiotics for AAD, including which strains have evidence for efficacy in AAD, what doses have been demonstrated to be effective, and the optimal duration of probiotic therapy, and provides practical guidance on how to select an appropriate product. Some trends emerged in this analysis of recent meta-analyses and systematic reviews, including: 1) Certain probiotics, such as *Saccharomyces boulardii* and some *Lactobacilli*-containing products, are consistently found to be effective for the management of AAD; 2) Dosing thresholds for efficacy exist that must be achieved through the administration of probiotics that reliably contain the labeled amounts of probiotic constituents; 3) Most effective probiotics are initiated at the same time as antibiotic therapy and continued for between 1 and 3 weeks after the cessation of therapy. These data suggest that attention must be paid to species, dose, and duration when selecting an appropriate product for patients initiating antibiotic therapy; further considerations may include the antibiotic used and the patient's baseline risk for AAD.

Keywords

Probiotics, AAD, *Saccharomyces boulardii*, *Lactobacilli*

1. Introduction

The human microbiome is a community of microorganisms that can be found

nearly everywhere in the body but is particularly dense and complex in the luminal spaces of the gastrointestinal (GI) tract [1]. The most recent estimates suggest that a person of average size and weight contains 30 trillion human cells and 39 trillion bacteria—a greater than 1 to 1 ratio of human cells to microbes [2]. It is thus unsurprising that this community can have profound direct and indirect effects on human health.

The mechanisms by which the human microbiota exert these effects have been under intensive study for at least the last 5 decades; however, the first recorded use was in ancient China, where human feces were used to manage gastrointestinal complaints [3]. It was not until the early twentieth century that Elie Metchnikoff, a physician working at the Pasteur Institute, directly linked the consumption of certain fermented dairy products to human health [4]. The discovery of *Saccharomyces boulardii* in 1920 was a pivotal moment in probiotic history, marking the first time that supplementation with a specific species of microorganism was directly linked to protection against GI disease—in this case, diarrhea occurring as the result of a widespread cholera outbreak in Southeast Asia [5].

Today, probiotics have become an important part of self-care regimens for many people, with one recent (2021) survey of more than 13,000 consumers finding that nearly one-quarter had deliberately used a probiotic-containing product in the previous 6 months [6]. Probiotics have also become widely used in clinical practice, particularly for the management of GI disorders, as highlighted by recent guidelines published by the American Gastroenterological Association (AGA) [7]. They are widely available in various single- and multiple-organism products administered orally in a manner analogous to conventional pharmaceuticals or in combination with a variety of foods.

The World Health Organization defines probiotics as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [8]. Probiotics have been more precisely defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP) as "live microorganisms with a suitable viable count of well-defined strains with a reasonable expectation of delivering benefits for the wellbeing of the host" [9]. Unfortunately, the marketplace has hundreds or even thousands of products labeled as "probiotics" but that do not meet even these minimal criteria. Furthermore, claims have proliferated for these agents, and they have been marketed both for biologically and clinically plausible uses, such as for antibiotic-associated diarrhea (AAD), as well as for disease states in which their use is supported by limited and contradictory evidence at best. The lack of strong evidence for their use in most GI conditions has been highlighted by the AGA guidelines, which give "conditional" recommendations, or no recommendation at all, for their use in many disease states [7].

AAD is well recognized to be associated with increased morbidity and mortality, prolonged hospital admissions, and a high cost of care [10] [11] [12] [13]; further, it is also an important reason for premature antibiotic discontinuation

[14]. Thus, readily accessible adjunctive therapies that can reduce the risk for AAD or limit its duration are highly desirable. In contrast to the limited evidence available for the efficacy of probiotics in other disease states, a broad consensus has emerged that these products may be effective in the prevention of AAD in general and/or *Clostridioides difficile*-associated diarrhea (CDAD) specifically, leading to guideline recommendations of varying strengths in this setting [7] [15] [16].

The strength of the evidence for specific probiotic strains and formulations for AAD varies widely, and there are still gaps in knowledge. Perhaps more than any other product used routinely to affect human health, probiotics cannot be considered a homogeneous class, and the potential clinical benefits and risks of these products probably vary by strain and dose [7]. Thus, if a therapeutic effect is desired, considerable care must be taken to select products with a clearly defined composition, appropriate viable counts, and evidence for health benefits. Guidelines recognize this heterogeneity by recommending only specific probiotic formulations [7] [16]. Although less well addressed in guidelines, it would be expected that—like any product with a clinical effect—it is critical to administer these agents at doses and for durations that are most likely to have a therapeutic benefit. This paper seeks to fill some of the knowledge gaps.

Here, we focus on the utility of probiotics in AAD to clarify some outstanding issues regarding their use for this indication. Given their inherent low risk for adverse events (AEs); the consistent, albeit moderate-quality, evidence for the benefits of probiotics in the prevention of AAD; and their low cost (relative to the cost of managing AAD), we attempt to address whether carefully selected probiotics, administered in doses and durations according to best available evidence, should be a routine part of care in patients who are prescribed antibiotics.

2. Antibiotic-Induced Alterations in the Gut Microbiota

Antibiotics are well-known to perturb the normal GI microbiota, opening niches where pathogenic bacteria can thrive and resulting in diarrhea [17]. Antibiotics are likely not a homogeneous class in terms of their effects on the microbiota, and the risk for AAD may vary by mechanism of action, spectrum of activity, duration of treatment, and other factors [18]. Thus, it is difficult to draw any firm conclusions on the effect of an individual antibiotic on the composition of the microbiome.

One meta-analysis of studies evaluating common antibiotics for upper respiratory and urinary tract infections found that all antibiotics suppressed bacterial diversity and resulted in substantial shifts in the microbiota composition [19]. However, generalization of the effect of antibiotics was hampered by methodologic inconsistencies and a failure to consistently define normal baseline microbiota composition. A second systematic review of 129 studies also found widely disparate effects of antibiotics on the gastrointestinal microbiota, including impacts on species and taxa that would be expected to be associated with an increased risk for AAD [18]. Some studies have reported the time for the gut mi-

crobiota to recover to baseline; in these studies, the time to restoration to baseline ranged from 6 to 8 weeks after stopping aminoglycosides to between 1 and 4 years after ciprofloxacin, clindamycin, and clarithromycin in combination with metronidazole [18].

It is clear most antibiotics have significant, albeit disparate, effects on the gut microbiome. These differential effects on the microbiome may translate to different risks for AAD. Clinically, data from a study conducted in hospitalized patients suggest that β-lactams are associated with substantially higher rates of GI AEs (defined in this study as the composite of nausea, emesis, and non-*C. difficile* diarrhea; 17.4/10,000 person-days) as compared with non–β-lactams (ranging from no GI AEs to 12.4/10,000 person-days) [20]. Although most β-lactams in this analysis were associated with relatively high rates of AAD, some, such as oxacillin, were associated with rates above 30/10,000 patient-days. Of the non–β-lactams, only doxycycline (12.4/10,000 person-days) and trimethoprim-sulfasalazine (11.2/10,000 person-days) approached the rates seen with most β-lactams. The rates reported in this study are probably substantial underestimates of the true incidence of AAD by class, as the underlying data were derived from a hospital with an active antibiotic stewardship program that likely had a strong influence on both the use and duration of antibiotic treatment, with a resulting reduction in the overall incidence of AAD. It is important to emphasize that because these data reflect only hospitalized patients, they may not reflect the incidence of diarrhea in the outpatient population, which may often go unreported.

Although evidence is limited on which to base firm recommendations, it is possible that patients treated with certain antibiotic classes, such as β-lactams, may benefit most from proactive use of probiotics to prevent diarrhea, with initiation at the same time as antibiotic therapy and continuation for at least several weeks thereafter. This strategy is also supported clinically by the meta-analyses discussed below. While the methodologic issues with attempting to synthesize these data limit interpretation, both the microbiologic and clinical data point toward differential effects of antibiotics on gut microbiota. All antibiotics likely cause at least some degree of microbial perturbation (dysbiosis) that lasts weeks to years after cessation of antibiotic treatment. Among patients treated with antibiotics known to result in extended disruption of the GI microbiome, more prolonged administration periods following antibiotic cessation are at least biologically plausible, although there is no strong clinical evidence for or against this strategy.

3. How Do Probiotics Treat AAD?

Selected probiotics have consistently shown efficacy in AAD. However, the mechanisms by which they exert these activities remain under active investigation and are in some cases unclear [3] [17] [21] [22]. Again, it is important to emphasize that probiotics are highly heterogeneous, and the effects of one probiotic on various parameters do not necessarily indicate that other probiotics will have the same effects.

Until recently, it was thought that probiotics do not colonize the GI tract. However, recent evidence suggests that some may become long-term residents of the GI tract—at least in some people and under some conditions. One recent study evaluated whether twice-daily administration of bacterial probiotic to healthy volunteers was associated with colonization or changes in host microbiota function [23] [24]. In this study, some probiotic strains persistently colonized the GI mucosa; however, inter-individual differences were detected. Approximately half of the participants were "permissive" to colonization, and in these patients, probiotic strains were detectable at 3 weeks post-administration. The other half were "resistant" and showed no sign of colonization. In a second study using the same probiotic strains, 1 week of ciprofloxacin and metronidazole was administered to healthy subjects to eliminate their microbiome; these subjects were divided into a control group, a fecal transplant group, and a group that received 4 weeks of treatment with the study probiotic. Among those who received probiotics, there was clear evidence for colonization by probiotic strains and reconstitution of the baseline microbiota was delayed [25]. This finding is consistent with the hypothesis that destruction of the native microbiome opens niches that probiotic strains can occupy, potentially augmenting the community of commensal bacteria that existed prior to antibiotic treatment and resulting in a long-term shift in gut microbe composition [23]. This replacement, whether temporary or long-term, may contribute to the reduction in risk for post-anti-biotic diarrhea seen with some probiotic products.

Aside from their potential ability to colonize and replace commensal bacteria destroyed by antibiotic treatment, several other mechanisms have been advanced for the effects of probiotics in AAD. Some of the more plausible effects are summarized in **Table 1**, although it should be cautioned that this is not a comprehensive review of postulated probiotic mechanisms of action, which have been discussed in detail elsewhere [26].

4. Probiotics for AAD

A broad range of single- and mixed-species probiotics are currently marketed for an equally broad array of health claims. As outlined earlier, it is clear probiotics should not be considered a homogeneous class. Indeed, for every product with evidence for efficacy in AAD, there are many more with little, if any, supporting data. Probiotics that have most often been the subject of study in appropriately designed clinical trials include single species or mixtures of *Saccharomyces boulardii*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Bifidobacteria bifidum*, *Bifidobacteria longum*, *Streptococcus thermophilus*, and *Clostridium butyricum* [27]. However, many other species and mixtures also have been evaluated.

Given the heterogeneity in study designs and patient populations, it is challenging to derive precise guidance on the selection and clinical use of probiotics from individual studies. However, there are some consistencies across studies

Table 1. Selected mechanisms of action of probiotics in AAD.

Competitive exclusion	May outcompete pathogenic bacteria by consuming nutritional resources, producing antibacterial molecules, or modulating the pH of the gastrointestinal macroenvironment. [26]
Effects on intestinal SCFAs	May maintain SCFA (acetate, propionate, and butyrate) concentrations during antibiotic use, reducing diarrhea by promoting sodium and water absorption. [21]
Effects on bile acid concentrations	Some probiotic strains may attenuate antibiotic-induced increases in colonic primary bile acids that may increase susceptibility to *Clostridioides difficile* infection. [21] [36]
Effects on barrier function	May prevent antibiotic-induced disruption in the intestinal barrier. [21] [37]
Immune effects	May reduce antibiotic activation of inflammatory pathways. [21] [26] *Lactobacillus* and *Saccharomyces*-based probiotics may upregulate the innate and adaptive immune systems. [28]

AAD = Antibiotic-Associated Diarrhea; SCFA = Short-Chain Fatty Acid.

that meta-analyses and systematic reviews have uncovered. These data can guide treatment choice, dose, and duration of therapy in the absence of large-scale, randomized, placebo-controlled studies.

4.1. What Is the Efficacy of Probiotics for AAD?

The efficacy of probiotics has been evaluated in several recent meta-analyses and systematic reviews for CDAD specifically and for the broader category of AAD regardless of causative organism [27] [28] [29]. These analyses consistently show that certain probiotics are effective in diarrhea prevention, with the effect often being driven by patient subgroups at higher baseline risk for these events.

A meta-analysis conducted by Goldenberg and colleagues explored the efficacy of probiotics in CDAD [29]. The analysis included 39 studies overall (9955 participants); among the 31 adequately conducted trials, probiotics were associated with a 60% reduction in risk for CDAD (1.5% with probiotics vs 4.0% with placebo or no treatment; risk ratio [RR] 0.40; 95% CI, 0.30 - 0.52). Per the results of a post-hoc analysis, probiotics were only effective in reducing risk for CDAD in high-risk patients. The authors noted that probiotic prophylaxis would prevent 85 CDAD episodes per 1000 patients at high risk for CDAD.

These data suggest that probiotics have a large protective effect against CDAD that is particularly evident in patients who are at high baseline risk for the disease; however, this species—despite being the single most commonly isolated organism in AAD—accounts for no more than 20% of all AAD cases [30]. A

second meta-analysis conducted by Goodman and colleagues sheds light on the efficacy of probiotics for AAD regardless of the causative organism. This analysis included 42 randomized, controlled studies of adults (N = 11,305) who received either a probiotic or a control or no treatment [28]. The outcome was the incidence of AAD. Overall, coadministration of probiotics with antibiotics was associated with a 37% reduction in the risk for AAD (RR 0.63; 95% CI, 0.54 - 0.73; $P < 0.00001$), although this effect was driven mainly by reductions in subjects at moderate to high baseline risk for AAD.

A third meta-analysis, conducted by Guo and colleagues examined the utility of probiotics for pediatric AAD prevention [27]. A total of 33 randomized, parallel, controlled pediatric trials were included (N = 6352) that compared probiotics with placebo, active alternative prophylaxis, or no treatment. Probiotics evaluated in these studies included single species or combinations of *Bacillus* spp., *Bifidobacterium* spp., *C. butyricum*, *Lactobacilli* spp., *Lactococcus* spp., *Leuconostoc cremoris*, *Saccharomyces* spp., or *Streptococcus* spp. Across all studies, AAD occurred in 8% of the probiotic group and 19% of the control group, corresponding to a 55% reduction in the risk for AAD (RR 0.45; 95% CI, 0.36 - 0.56). After accounting for patients who were lost to follow-up, the incidence of AAD was 12% in the probiotic group vs 19% for the control group (RR 0.61; 95% CI, 0.49 - 0.77; $P < 0.00001$). Among patients who developed diarrhea, probiotics were associated with a reduction in duration of 0.91 days (MD −0.91%; 95% CI, −1.38 to −0.44), although only 8 studies reported this outcome and thus, the evidence was considered low certainty.

The efficacy of probiotics does not appear to be compromised by an increased risk for AEs. Current meta-analyses consistently report few AEs, a similar risk for AEs to controls, or a reduction in AEs in the probiotics group relative to the control group, [27] [28] [29] although serious AEs have been observed in immunocompromised or severely debilitated patients [27].

4.2. Which Strains Are Effective?

The acute and chronic response of the microbiome to probiotics, and thus their impact on disease, will vary not only by product but also on an individual basis depending on the pre-existing composition of the microbiota, antibiotics used, and individual host factors [24] [25]. However, only some probiotics have consistently demonstrated efficacy in reducing AAD. Across recent meta-analyses, systematic reviews, and guidelines, *S. boulardii* was consistently identified as an effective probiotic, regardless of the population studied (adult or pediatric CDAD and adult or pediatric AAD) (**Table 2**) [7] [27] [28] [29] [31]. Probiotics containing *L. acidophilus*, often in combination with *L. casei*, were also frequently included among those probiotics considered effective for these indications.

4.3. What Dose Is Effective?

By definition, probiotics must be given in adequate amounts to achieve a health

Table 2. Effective probiotics according to recent meta-analyses, systematic reviews, and guidelines (Goldenberg 2017, Goodman 2021, Guo 2019, Sniffen 2017, Su 2020).

	Patient Population	Effective Probiotics	
		Yeast	Bacteria
Meta-analyses			
Goldenberg *et al.* 2017 [29]	Prevention of pediatric CDAD	• *S. boulardii*	• *L. acidophilus plus L. casei*
Goodman *et al.* 2021[a] [28]	Prevention of adult AAD	• *S. boulardii*	• *L. acidophilus* • *L. bulgaricus* • *L. casei* • *L. paracasei* • *L. rhamnosus* • *Lactobacillus* spp. • *B. animalis* ssp. *Lactis* • *B. longum* • *B. licheniformis* • *B. subtilis* • *Bac. clausii*
Guo *et al.* 2019 [27]	Prevention of pediatric AAD	• *S. boulardii*	• *L. rhamnosus*
Systematic Review			
Sniffen *et al.* 2018 [31]	Prevention of AAD	• *S. boulardii*	• *L. casei* DN114001 • 3-strain combination: *L. acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2
AGA Guideline			
Su 2020[b] [7]	Prevention of CDAD	• *S. boulardii*	• 2-strain combination: *L. acidophilus* CL1285 and *L. casei* LBC80R • 3-strain combination: *L. acidophilus*, *L. delbrueckii subsp bulgaricus*, *and B. bifidum* • 4-strain combination*: L. acidophilus*, *L. delbrueckii subsp bulgaricus*, *B. bifidum*, and *Strep. salivarius subsp thermophilus*

[a]Most studies in this analysis used probiotic formulations containing ≥ 1 probiotic species; a subgroup analysis was performed on all individual species mentioned in included studies. [b]Conditional recommendation; low-quality evidence: "patients who place a high value on the potential harms (particularly those with severe illnesses) or a high value associated on avoiding the associated cost and a low value on the small risk of *C. difficile* development (particularly in the outpatient setting) would reasonably select no probiotics." AAD = antibiotic-associated diarrhea; AGA = American Gastroenterological Association; *Bac.* = *Bacillus*; *B.* = *Bifidobacterium*; CDAD = *Clostridioides difficile*-associated diarrhea; *L.* = *Lactobacillus*; *S.* = *Saccharomyces*; *Strep.* = streptococcus.

benefit [8]. A universal "best dose" of these agents is difficult, if not impossible, to identify because of the inherent heterogeneity among products. Furthermore, it remains to be determined if there is a stringent dose-response relationship with probiotics; given that these are living organisms, it is unlikely that this relationship is as simple as it is for many conventional pharmaceutical products.

In some cases, the best doses of specific probiotics, such as the yeast *S. boulardii*, have been well defined through decades of clinical experience and clinical studies. Yeast-based probiotics are dosed in milligrams and the effective dose of

S. boulardii is typically 500 to 1000 mg/day. Evidence from meta-analyses can be used to guide effective dosing of some bacterially based probiotics. Although the data cannot be reliably generalized, there appears to be a threshold of approximately 5×10^9 CFU/day across many of the studies described here, above which efficacy is more often observed for bacterially based probiotics. In a subgroup analysis of the Goodman meta-analysis described earlier, dosages of 5×10^9 CFU/day were associated with a significant 46% reduction in the relative risk for AAD in 4 studies with adequate data (RR 0.54; 95% CI, 0.38 - 0.76; $P < 0.01$) [28]. The Guo pediatric meta-analysis found that high-dose ($\geq 5 \times 10^9$ CFU/day) probiotics were generally more effective than lower doses ($P = 0.01$) [27]. In this analysis, AAD occurred at a rate of 8% in the high-dose probiotic group vs 23% in the control group (RR 0.37; 95% CI, 0.30 - 0.46; $P = 0.00001$), whereas in the low-dose studies, the corresponding values were 8% and 13%, respectively (95% CI, 0.46 - 1.01; $P = 0.02$). The Sniffen systematic review identified a somewhat higher threshold of 10^{11} CFU/day for efficacy in AAD and a systematic review conducted by Ouwehand *et al.* found that doses above 10^{10} CFU/day were effective in this setting [31] [32].

4.4. How Long Should Probiotics Be Administered?

Given their broad use as preventive treatments in the setting of AAD, surprisingly few data are available on the appropriate duration of therapy in patients receiving antibiotics. In the Goodman meta-analysis, probiotics were administered for 5 days to 56 days; most probiotics were initiated concomitantly with antibiotics and continued for an additional week after completion of the antibiotic course [28]. In the Sniffen systematic review, most effective probiotics were started within a few days of antibiotic initiation and continued until 7 to 28 days following completion of the antibiotic course [31].

Studies of the long-term impact of antibiotics suggest that longer durations may be appropriate to provide adequate support during the period of time when the gut microbiota is compromised by antibiotic therapy and to facilitate a return to a stable state that may—or may not—reflect the baseline composition of the microbiota but that nevertheless is not associated with diarrhea. Facilitating rapid restoration of the gut microbiota to a stable, healthy state is desirable to close niches created by antibiotic therapy that may be filled by microbiota that are associated with a reduced benefit to the host [33] [34] [35].

4.5. Importance of Appropriate Probiotic Selection

Unlike the situation that pertains with FDA-approved branded conventional pharmaceuticals and their Orange Book-listed generic equivalents, it is critical to consider brand when selecting probiotics. Regardless of the probiotic chosen, quality control, manufacturing processes, stability over time, and formulation all play into the choice of an effective probiotic. Given that the probiotic market is largely unregulated, selection of probiotics from established manufacturers may be important. These products are more likely to be consistent from batch to batch, less

likely to include unlabeled strains/species, and are generally more likely to produce clinical results consistent with clinical data [31]. The label should adhere to certain minimum requirements; in addition to displaying the US Food and Drug Administration disclaimer, it should provide clear daily dose information, list the probiotic strains clearly, and not include unproven health claims [31].

5. Conclusions

As outlined here, recent meta-analyses consistently support the efficacy of probiotics for the prevention of AAD. However, there are wide disparities in the evidence underlying the efficacy of individual probiotics. Current meta-analyses, systematic reviews, and guidelines have consistently found that single-species *S. boulardii* probiotics are effective; certain *Lactobacilli* species are likely also effective for this indication, although the interpretation of these data is hampered by the fact that many of these probiotics are available only as complex mixtures.

The dosing and duration of therapy are as important as selecting products supported by evidence. Choosing a product that is likely to deliver the labeled dose of probiotics is critical. While few data are available to support the duration of therapy, the kinetics of microbiome recovery after antibiotic therapy suggest that it is reasonable to provide probiotic support for at least 1 to several weeks after antibiotic discontinuation.

Linking a specific probiotic product directly to the clinical evidence supporting its use can be challenging and more prospective studies are needed. On balance, recent meta-analyses, systematic reviews, and clinical guidelines provide adequate data to support the use of specific products for the prevention and management of diarrhea and it is important to emphasize that these results cannot be extrapolated to all products that call themselves "probiotics". Instead, it is critical to select products that are supported by existing evidence. It is also critical to understand that the efficacy of these products is highly dependent on quality control in manufacturing, thus it is important to select probiotics from trusted suppliers that meet FDA requirements for labeling.

Disclosures

John R Ferguson is a professional medical writer. He was compensated financially for assisting in the development of this publication. He has no other relevant disclosures.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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