Inflammatory Mediators in Intra-abdominal Sepsis

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2.1 Abdominal Sepsis, Inflammatory Mediators, and Possible Therapeutic Strategies

The current consensus definitions for sepsis have defined sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection" [3, 4]. This new definition emphasizes the primacy of non-homeostatic host response to infection. Yet, at present, there is no gold-standard diagnostic test for this syndrome, mainly due to the current challenges in the microbiologic confirmation of infection. Thus, the clinical criteria of "suspected infection," which include clinical signs and symptoms in a patient who requires antimicrobial treatment or body fluid culture, are suggested for operationalization proxies.

However, the clinical manifestations of sepsis are identical to those secondary to systemic inflammatory response syndrome (SIRS). The cause of SIRS can be infectious or noninfectious insults such as trauma, major surgery, acute pancreatitis, or

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M. Sartelli et al. (eds.), *Abdominal Sepsis*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-319-59704-1_2

burns. A major host response to these noninfectious insults is to release many endogenous mediators or damage-associated molecular patterns (DAMPs) that, like the microbial pathogen-associated molecular patterns (PAMPs), activate the immune system and initiate the inflammatory response that is responsible for the major lethality of sepsis as a result of multisystem organ failure (MSOF). For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone [4].

DAMPs and PAMPs share a number of conserved families of pattern recognition receptors (PRRs), including the prototypical PRR family, the toll-like receptors (TLRs). Activation of TLRs on immune cells and endothelial cells leads to the release of pro- and anti-inflammatory mediators, which are the

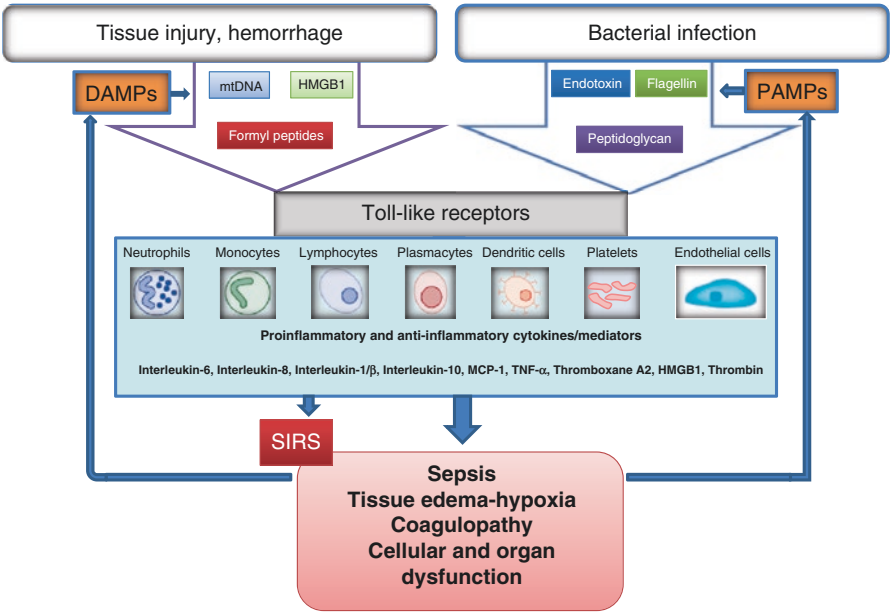

Fig. 2.1 Schematic pathways of injury and infection leading to systemic inflammatory response syndrome (SIRS) and sepsis. Tissue damage leads to the extracellular release of damage-associated molecular patterns (DAMPs). Infection is associated with exposure of the immune system to pathogen-associated molecular patterns (PAMPs). DAMPs and PAMPs stimulate cells of the innate immune system, which lead to release of pro- and anti-inflammatory mediators and endothelial damage, resulting in further tissue hypoxia, organ dysfunction, and immunoparesis causing persistent inflammation, immunosuppression, and catabolism syndrome (PICS), which lead to the release of further DAMPs and PAMPs. *HMGB1* high mobility group box 1 protein, *mtDNA* mitochondrial DNA, *TNF-α* tumor necrosis factor alpha, and *MCP-1* monocyte chemoattractant protein 1

effectors triggering excessive inflammation and multiple organ failure (Fig. 2.1) [5–7, 8]. Additionally, activation of platelets results in the release of additional pro-inflammatory molecules, modulates vascular tone, and can result in sepsis-associated coagulopathy [9, 10]. Activated platelets modify the effector functions of other immune cells including the induction of neutrophil extracellular trap (NET) release from neutrophils [11]. NETs are extracellular DNA structures comprised of decondensed chromatin decorated with both nuclear and granular proteins [12] and DAMPs. These "webs" are designed to catch and kill pathogens but are very cytotoxic, causing damage to surrounding tissues and further potentiating coagulation. Multichannel molecular mediators will likely to better characterize specific subsets of sepsis. They may be used as biomarkers to differentiate sepsis from noninfectious insults and provide new therapeutic approaches.

2.2 Abdominal Sepsis

Intra-abdominal sepsis (IAS) is a continuing challenge as it remains frequent, being the second most common cause of sepsis with high mortality rates, and in particular it can be difficult to distinguish sepsis from "sterile" SIRS, and delays in recognizing "failed source control" can often be fatal although it is often a very difficult task [13, 14]. Despite advances in diagnosis, surgery, and antimicrobial therapy, mortality rates associated with complicated intra-abdominal infections and intra-abdominal sepsis remain exceedingly high [15]. As recommended by the World Society of Emergency Surgery (WSES), patients with sepsis or septic shock of abdominal origin require early hemodynamic support, source control, and antimicrobial therapy [16]. Despite many practical recommendation regarding interventions and support, the WSES also noted that the progression to septic shock is characterized by excessive inflammation.

2.3 Inflammatory Mediators and Potential Compartmentalization

Emr and colleagues have suggested that multi-organ dysfunction syndrome (MODS) occurs because of cascading system failure, wherein the positive feedback loop of inflammation drives tissue damage, which propagates inflammation that exceeds compartment-specific thresholds [17]. In terms of abdominal infections, the relevant compartments are the local ascites and the distant systemic endothelia, particularly that in the lungs. The pathways between these compartments *include* mesenteric lymph and the systemic circulation (Fig. 2.2). This conceptualization of interrelated compartments and sepsis is congruous with the WSES clinical concept in which an uncomplicated case of abdominal infection only involves a single organ and does not extend to the peritoneum [15, 16].

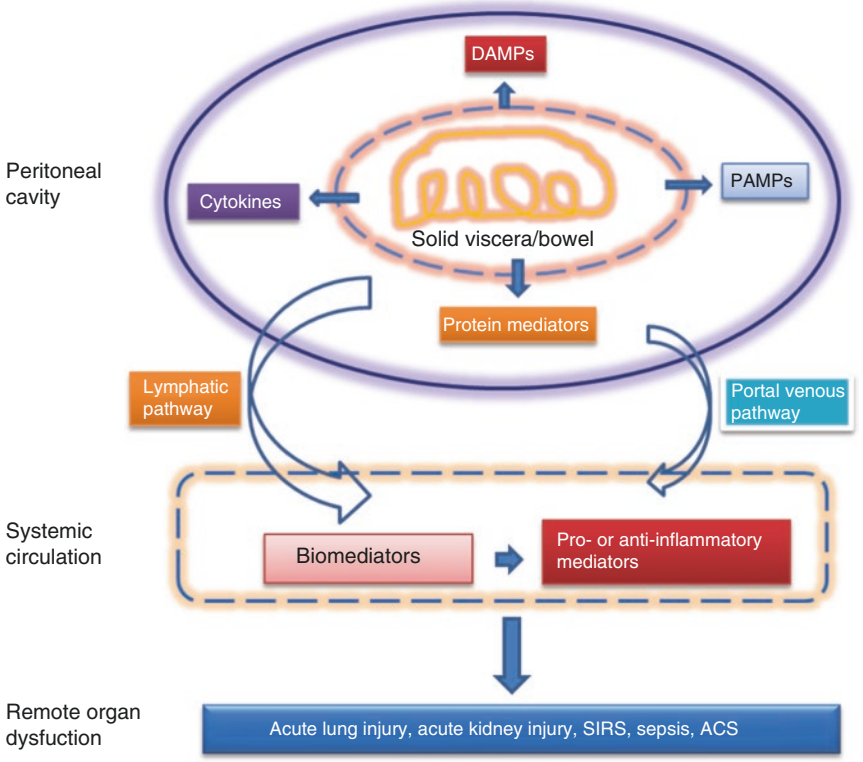

Fig. 2.2 Schematic important pathways of biomediators entering systemic circulation from inflammatory peritoneal fluid, leading to remote organ dysfunctions. *ACS* abdominal compartment syndrome

2.4 Serum Biomediators in Abdominal Sepsis

The reasons to study inflammatory mediators (IMs) include (1) to better understand the basic pathogenesis of sepsis and injury-related organ dysfunction; (2) to provide earlier diagnoses of sepsis syndromes and predict complications or outcomes, especially "failed source control"; and (3) to determine therapeutic targets for randomized controlled trials (RCTs) of sepsis modulating agents [8]. Despite this, the identification of therapeutic targets and development of sepsis modulating drugs have been an expensive and frustrating process thus far. There have been literally hundreds of failed anti-mediator trials, and thus the developmental pipeline for novel therapeutics for treating sepsis has diminished to a trickle with the one potential drug activated protein C (APC) being taken off the market [18]. It has become readily apparent from these failed anti-mediator trials that the attempt to neutralize, block, or promote a single biomediator after they have been generated is not helpful [19].

Xiao and colleagues recently extensively reviewed inflammatory mediators (IMs) in intra-abdominal sepsis and/or injury [8]. The overriding message of this review was one that De Waele independently concluded in his contemporary summary of abdominal sepsis [14]:

> …while preclinical data suggest that inflammatory mediators play an important role in intra-abdominal sepsis and injury, ultimately there is **NO** consensus on the clinical use of inflammatory mediators in diagnosing or managing intra-abdominal sepsis, their exact role remains incompletely understood.

To derive this message, 182 studies were retained that assessed or discussed IMs in relation to intra-abdominal sepsis or injury out of 2412 potential studies screened [8]. Another high-level summary of the overall conclusions was that before 1992 C-reactive protein remained the most studied IM. After 1992, the interleukins and tumor necrosis factor (TNF) were primary foci of interest. After 2000, procalcitonin was investigated, and until most recently, DAMPs and endothelial dysfunction molecules have been focused upon in the reported English language literature.

2.4.1 C-Reactive Protein

At the time of writing, at least 33 studies have evaluated CRP in relation to IAS. In general, CRP levels elevate on postoperative day (POD) 1, peak from POD2 to POD3, and decline by POD5 provided there is no complication or infection. While four reports suggest that a persistent threshold of greater than 100 mg/l might indicate abscess/septic complications [20–23], other studies have refuted this conclusion, leaving uncertainty for clinical practice [24–28].

2.4.2 Procalcitonin

Twelve trials, including two RCTs, have evaluated procalcitonin. In general, levels increase immediately after surgical injury, peak on POD 1, and decline to half its peak level from POD2 to POD3 after uncomplicated abdominal surgery. Again, in some reports persistently high levels have been associated with infection and/or increased septic mortality in patients with sepsis [21, 26, 29, 30], but not consistently enough to be adopted for use in clinical practice [31, 32].

2.4.3 IL-6

Like in most areas of sepsis, IL-6 is one of the most commonly studied markers. The plasma levels are rapidly dynamic. They peak from wound closure to POD1 and then return to baseline by POD3. The role of IL-6 as a marker to diagnose sepsis or

predict outcomes remains uncertain, with wide range of cutoff values suggested (from 12 to 2760 pg/ml). One of the most recent published studies (retrospective review of prospectively captured samples), which compared CRP, IL-6, and TNF levels after major abdominal surgery, noted that IL-6 as a single test had early prognostic information by day 1 with an area under the curve of 0.67, although CRP started to discriminate from day 3 onward with an improved area under the curve of 0.73 [33].

2.4.4 Damage-Associated Molecular Patterns

DAMPs are early pro-inflammatory mediators released from damaged host cells upon lysis or injury, such as high mobility group box protein 1 (HMGB1), which is elevated in plasma early in shock. DAMPs signal for necrotic cell clearance by phagocytic cells of the immune system. Freely circulating DAMPs may trigger an inflammatory reaction, much in the same fashion as pathogen-associated molecular patterns found on many bacterial pathogens, by binding to host cell receptors on a variety of immune cells. Some DAMPs, such as HMGB-1, have been shown to be both markers of damage and mediators of inflammation in sterile and non-sterile injury [34–36]. These have promise in IAS, but much more needs to be learned about them.

2.4.5 Interventional Trials

Despite the marked resources expended on attempting to find a pharmacologic solution for sepsis, there have only been nine such clinical interventions for abdominal sepsis, of which four were randomized controlled trials. One was our own RCT of peritoneal vacuum therapy [37, 38], which will be later discussed. Three concerned open versus minimally invasive techniques for treating seemingly less complex cases of sepsis related to appendicitis, cholecystitis, and perforated peptic ulcer [39–41]. Overall, there is unfortunately no clear message for clinicians to measure and especially to try to manipulate IMs to influence the outcome of abdominal sepsis at the current time.

2.4.6 Inflammatory Ascites

In contemporary critical care medicine, low-density peritoneal fluid (PF) is typically assumed to be benign. However, upon careful scientific scrutiny, the free intraperitoneal fluid found in critical illness actually more resembles a hostile sea of inflammatory mediators and toxins that may be a primary driving force for systemic sepsis and resultant multi-organ failure [17]. It has been found that increased levels of both systemic and peritoneal cytokines are associated with postoperative complications, which may discriminate survivors from those dying [42–45]. Although data

from research with animal models [44], inflammatory bowel disease [46, 47], and surrogate outcomes [48] are suggestive, direct evidence does not yet exist to prove that more efficiently draining this fluid will make a difference to complications or survival. Therefore, as a tantalizing area of current research, this topic should be further reviewed.

2.4.7 The Implications of Inflammatory Ascites

Severe intra-abdominal hypertension (IAH) has been shown to directly lead to multisystem organ failure in animal models [49, 50]. Grade III [defined as an intra-abdominal pressure (IAP) of 21–25 mmHg] and IV (IAP >25 mmHg) IAH has been shown to significantly reduce perfusion to the intestinal mucosa, which ultimately increases intestinal permeability and results in systemic endotoxemia and irreversible damage to the mitochondria and necrosis of the gut mucosa [50]. This disruption of the intestinal mucosal barrier may be one of the important initial factors responsible for the onset of abdominal compartment syndrome (ACS) and the impetus for the development of multi-organ dysfunction syndrome [49, 50]. For years it has been postulated that the damaged gut is a continual source of inflammation and MODS, referred to as the "Motor of MSOF" [51–56], by inducing the production of cytokines and other biomediators and propagating acute respiratory distress syndrome (ARDS). The release of endotoxin induces production of cytokines, including IL-6, IL-1β, IL-8, TNF-α, and other mediators. Movement of these mediators into the systemic circulation may possibly be largely facilitated through the mesenteric lymphatic channels [57]. This movement initiates pulmonary damage and development of acute respiratory distress syndrome (ARDS) [17, 51, 52, 54–56, 58]. Further, circulation of these mediators results in systemic inflammation.

With critical abdominal illness and surgery, there is a remarkably active biomediator response in the local peritoneal environment. One study comparing intraperitoneal cytokine levels in patients who required abdominal surgery for active inflammatory bowel disease (n = 50), colorectal cancer (n = 25), and appendicitis (n = 25) found that intraperitoneal cytokines were significantly elevated in the patients with inflammatory bowel disease [46]. Very notably, commonly used systemic inflammatory markers (e.g., the white blood cell count) showed no correlation with the measured cytokine levels. Intraperitoneal cytokines were also significantly higher in patients with postoperative septic complications than in those without such complications, suggesting that their measurement might potentially predict earlier which patients would be at the highest risk for such complications. The authors therefore suggested that levels of intraperitoneal cytokines might better stratify the degree of intraperitoneal inflammation and guide local therapy for the prevention of postoperative septic complications [46], a capability certainly not yet possible with serum IMs. A further prospective study measuring intraperitoneal cytokines on the first 3 postoperative days in patients who had elective colorectal surgery (n = 100) found that key cytokines (IL-1β, IL-6, and TNF) were significantly increased in patients with postoperative sepsis (n = 8) and significantly

decreased in patients without sepsis ($n = 92$), implicating these mediators as potential early markers of peritonitis [47].

A laboratory study assessed the biological activity of peritoneal fluid from swine with intra-abdominal sepsis using peritoneal fluid collected 12 h after induction of ischemia/fecal sepsis [48]. The study used peritoneal fluid from either septic or control animals to prime naïve human neutrophils and then measured neutrophil superoxide production and surface antigen expression. Levels of IL-6 and TNF-α in peritoneal fluid were also measured and found to be significantly increased in the sepsis group compared with the control group. The study demonstrated that in the face of sepsis, peritoneal fluid may greatly increase the pro-inflammatory characteristics of abdominal cavity-derived lymph flow [48]. The authors suggested that such sepsis-primed neutrophils may make patients more susceptible to any second insult, such as pneumonia or bleeding [48]. They also recommended that future research should investigate whether early removal of inflammatory ascites downregulates local and/or systemic inflammation or alters pro-inflammatory characteristics of mesenteric lymph [48].

Further laboratory work has associated increased intraperitoneal cytokines with adverse outcomes. Such associations in secondary peritonitis were investigated in a rat model of induced peritonitis [44]. Measurement of intraperitoneal mediators at 24 and 72 h found that intraperitoneal cytokine levels (IL-6, TNF-α, and IL-10) significantly predicted survival [44]. The gross predictive value of such measurements also seems consistent at the bedside. A human study of 29 burn patients with severe IAH/ACS measured cytokine levels in the peritoneum and in plasma and found that mortality was associated with increased interferon-γ, IL-10, IL-6, IL-4, and IL-2 in peritoneal fluid [59]. A study in 34 elective colorectal surgery patients compared cytokine levels in patients with anastomotic leakage ($n = 4$) with those who had no leakage ($n = 30$) [60]. Peritoneal cytokine levels progressively decreased in those without anastomotic leakage and progressively increased in those with leakage or peritonitis [60].

Thus, there appears to be circumstantial evidence that intraperitoneal cytokines are likely involved in the production of poor outcomes in critical illness/injury and even if not causal are at least markers of harmful processes. Mechanistically, there does also appear to be compartmentalization of these processes, meaning that local environments of mediators may be different from other compartments and their influence on the systemic outcomes dependent on tipping points such as transport factors [61]. Thus, hemoadsorption in a rat model of gram-negative sepsis appears to re-compartmentalize inflammation and reduce organ dysfunction [62].

2.5 Preventing Systemic Dissemination of Intraperitoneal Inflammatory Mediators

In regard to IAS, the internal flow of mesenteric lymph may serve a crucial previously underappreciated role. A canine study of the effect of mesenteric lymph duct ligation in an inflammatory injury model of portal vein occlusion and reperfusion

compared with portal vein occlusion and laparotomy only found significantly decreased lung injury and decreased TNF-α, IL-1β, and endotoxin in thoracic duct lymph in dogs with lymphatic duct ligation, but not in those with portal vein occlusion, indicating that cytokines reached the systemic circulation through the lymph [63]. In addition, a rat study of mesenteric lymph diversion in an ischemia-reperfusion model found significantly increased lung injury in animals with an intact lymphatic duct compared to those whose lymphatic duct was ligated [57]. Finally, a canine model assessing the effect of primary (originating because of diseases in the abdominopelvic cavity) and secondary (originating because of diseases or conditions outside of the abdominopelvic cavity) IAH on hemodynamics, intestinal fluid balance, and mesenteric lymph flow found that secondary IAH increased lymph flow and contributed to the development of gut edema, supporting the importance of abdominal decompression to prevent mediator release and entry into the lymphatic circulation [64].

Given the potentially profound consequences emanating from the generation, accumulation, and eventual dissemination of biomediators from the peritoneal space, investigators have sought to remove or block them at the source. An elegant laboratory study utilized barrier prevention methods *within* the peritoneal cavity. Narita studied an ischemia-reperfusion model of intestinal ischemia, involving three groups consisting of controls (no ischemia) compared to 90 min of ischemia followed by 180 of reperfusion versus the same ischemia-reperfusion model except with bowel isolation in a condom [65]. Remarkably, it was noted that the bowel isolation group had lower plasma cytokine levels (IL-β, TNF, IL-8) and reduced lung injury compared to the non-isolated ischemic group [65].

2.6 Practical Bedside Approaches to Inflammatory Ascites Drainage

Based on biological plausibility, it appears reasonable and possibly desirable to remove ascites from the severely ill and injured with sepsis or SIRS when it can be safely performed. Realistically, placement of barrier precautions around ischemic/leaking viscera or lymphatic ligation is not clinically practical. In clinical practice, the accumulation of intraperitoneal mediators can be removed by either percutaneous drainage or negative pressure therapy with an open abdomen. Percutaneous drainage is recommended to treat intra-abdominal hypertension if it is possible to safely perform, as it may obviate the need for decompressive laparotomy [49, 66, 67]. We are not aware of data confirming that percutaneous drainage removes inflammatory ascites and improves outcomes in patients with sepsis or SIRS, and such work should be conducted. If percutaneous drainage is not safely possible, negative pressure peritoneal therapy (NPPT) may be another appropriate option if the patient already has an open abdomen. NPPT involves the application of a continuous suction action to the peritoneal cavity through specially designed temporary abdominal closure systems with visceral-protective covers containing multiple suction channels.

There exists animal data suggesting that NPPT may profoundly ameliorate the overall system effects of inflammatory ascites and its causal conditions. A comparison of NPPT therapy with passive drainage in a porcine sepsis model found that NPPT removed inflammatory ascites and cytokines better than passive drainage, thereby reducing circulating cytokines and greatly improving organ function [17, 68]. While the study of inflammatory ascites and its constituents is in its infancy, there is a clinical signal that NPPT may benefit the critically ill. Cheatham et al. [69] compared the more efficient commercial NPPT system with one that is potentially less efficient, the Barker's vacuum pack. This non-randomized study included 280 patients, of whom 168 had 48 h of TAC therapy. The 30-day all-cause mortality was 14% for the commercial system and 30% for Barker's ($p = 0.01$). While the non-randomized design cannot confirm causality, reasons postulated for the improved result may be improved peritoneal drainage with a more uniform suction effect with the commercial system [69]. A recent systematic review of negative pressure therapy for critically ill adults with open abdominal wounds found two randomized controlled trials and nine cohort studies (three prospective and six retrospective) that met inclusion criteria [70]. The review concluded that limited prospective comparative data suggested that negative pressure therapy may be linked with improved outcomes compared with alternative temporary abdominal closure (TAC) techniques. Clinical heterogeneity and the quality of the studies precluded definitive conclusions. It was concluded that further randomized controlled trials are urgently required [38].

Subsequently an RCT was conducted in critically ill and injured patients with an average APACHE score of over 22 in patients with sepsis and an average ISS of over 23 in the injured. This study compared the same more efficient commercial NPPT system to the Barker's vacuum pack [71]. Although this study did not find a difference in actual peritoneal fluid drainage or in the behavior of the high-level mediators examined (IL-1β, IL-8, IL-10, or IL-12 p70 or tumor necrosis factor α), there was a survival difference in favor of the commercial system which is currently unexplained. It is possible that patient heterogeneity in the complex setting of mixed critical care populations solely explains the findings, and thus further studies are required.

Conclusions

Sepsis is a syndrome with an incompletely understood process. At present, there are no unambiguous clinical criteria or laboratory markers to uniquely distinguish sepsis from noninfectious insults. Overall the current state of science still has a limited understanding of the complete complexity of the effects, counter-effects, and interactions and effects of IMs in abdominal sepsis. Their serum measurement cannot yet be routinely recommended on clinical grounds. Conversely the measurement of intraperitoneal mediators appears to be a promising area of both scientific study and potentially a target for clinical guidance and potential intervention. However, the evidence is as yet mostly circumstantial, and further studies likely with more homogeneous populations will be required.

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