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High risk and low prevalence diseases: Metformin toxicities

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ABSTRACT

Introduction: Metformin toxicity is a rare but serious condition that carries with it a high rate of morbidity and mortality.
Objective: This review highlights the pearls and pitfalls of metformin toxicity, including diagnosis, initial resuscitation, and management in the emergency department (ED) based on current evidence.
Discussion: Metformin is a common medication used for treatment of diabetes mellitus. Metformin toxicity is a spectrum of conditions that may be differentiated into three subgroups: metformin-associated lactic acidosis (MALA), metformin-induced lactic acidosis (MILA), and metformin-unrelated lactic acidosis (MULA). MILA is a condition found predominantly in patients chronically taking metformin or those with large acute overdoses. Conversely, MULA occurs in patients on metformin but with a critical illness stemming from a separate cause. MALA is rare but the most severe form, with mortality rates that reach 50%. Differentiating these entities is difficult in the ED setting without obtaining metformin levels. Patients with metformin toxicity present with nonspecific gastrointestinal symptoms and vital sign abnormalities. Laboratory analysis will reveal a high lactate with anion gap metabolic acidosis. Patients presenting with elevated lactate levels in the setting of metformin use should be considered at risk for the most severe form, MALA. Patients with MALA require aggressive treatment with intravenous fluids, treatment of any concomitant condition, and early consideration of hemodialysis, along with specialist consultation such as nephrology and toxicology.
Conclusions: An understanding of metformin toxicity can assist emergency clinicians in diagnosing and managing this potentially deadly disease.

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1. Introduction

This article series addresses high risk and low prevalence diseases that are encountered in the emergency department (ED). Much of the primary literature evaluating these conditions is not emergency medicine focused. By their very nature, many of these disease states and clinical presentations have little useful evidence available to guide the emergency physician in diagnosis and management. The format of each article defines the disease or clinical presentation to be reviewed, provides an overview of the extent of what we currently understand, and finally discusses pearls and pitfalls using a question and answer format. This article will discuss metformin toxicity. This condition's low prevalence but high morbidity and mortality, as well as its variable atypical patient presentations and challenging diagnosis, makes it a high risk and low prevalence disease.

1.1. Terminology and pathophysiology

Metformin is one of the most prescribed medications for diabetes mellitus and is generally considered safe with few serious adverse effects. However, several major adverse events may occur with metformin. The most serious complication is metformin-associated lactic acidosis (MALA), with mortality ranging from 25 to 50% [1]. This term classically includes *any* patient on metformin with a rise in lactate. However, Lalau et al. 2017 proposed a spectrum of clinical conditions to include MALA, metformin-induced lactic acidosis (MILA), and metformin-unrelated lactic acidosis (MULA) [2]. MILA occurs when high serum levels of metformin are the primary cause of patient illness. Acute overdose with doses over 20 g or subacute accumulation due to renal failure can result in MILA. MALA occurs when an acute critical condition (e.g., sepsis, cardiogenic shock, stroke) develops in a patient on metformin, and there is no acute overdose of metformin. In MALA,

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metformin increases the degree of lactic acidosis, but only as a contributor, not as the sole cause. MULA occurs with a critical illness despite low metformin serum levels, and thus the lactic acidosis is due to a cause other than metformin.

Lactic acidosis and hyperlactatemia in the setting of metformin use are two distinct but commonly confused metabolic processes. Hyperlactatemia (a rise in lactate level) is the end product of pyruvate that is shunted to the anaerobic pathway. This does not create excess hydrogen ions and will not lead to an "acidosis." It is functionally an imbalance between production and utilization in oxygen-depleted states such as exercise [3]. Conversely "lactic acidosis" results in a true decrease in pH as well as hyperlactatemia. In metformin overdose settings, acidosis is the result of excess hydrogen ion accumulation from inhibition of the mitochondrial electron transport chain (ETC) [3]. If the mitochondrial ETC is not functioning appropriately, NADH increases, and pyruvate is converted to lactate.

Metformin has an oral bioavailability of 40–60% and is rapidly absorbed within 6 h of ingestion, with a half-life of 2–9 h [4]. Once absorbed, 90% is renally excreted unchanged. The therapeutic concentration of metformin is 0.5–3 mg/L. The lethal plasma concentration is >50 mg/L, and the toxic dose is >5 g in adults and > 100 mg/kg in pediatric patients. Patients with significant renal disease will predictably have a prolonged half-life of metformin and are at greater risk of metformin toxicity [3]. Therapeutically, metformin has a variety of mechanisms by which it decreases blood glucose. First, it enhances inhibition of gluconeogenesis by both insulin and glucagon. Metformin also improves insulin receptor phosphorylation and tyrosine kinase activity, which facilitates glucose transport into the cell via its effect on the glucose transporter and decreases insulin resistance in hepatocytes and adipocytes [3]. The most common adverse events associated with metformin include nausea, vomiting, and diarrhea, experienced in up to 25% of patients [5,6]. However, prior literature from 1996 suggests that for every 100,000 patient-years of exposure to metformin, there are approximately 10 events of severe MALA with similarly cited mortality rates reaching 50% [7]. These conditions involving metformin are generally poorly understood, and management varies based on the patient presentation, particularly if there are coexisting causes of hyperlactatemia. This article aims to guide initial emergency department (ED) recognition and management of hyperlactatemia believed to be metformin-related based on recent evidence-based recommendations.

2. Discussion

2.1. Presentation

The typical presentation of metformin toxicity includes nausea/vomiting, abdominal pain, decreased oral intake, diarrhea, and/or altered mentation. This presentation is nonspecific and can mimic many other disease presentations. Vital sign abnormalities may include tachycardia, tachypnea, hypothermia, and/or hypotension. Whenever metformin is noted in the history or on a medication list, the clinician should consider metformin toxicity. In the setting of renal insufficiency, and thus decreased metformin clearance, these symptoms are often magnified [3,7].

2.2. ED evaluation

Patients evaluated in the ED should undergo a focused history. A comprehensive review of the patient's current and prior medications is necessary. For patients prescribed metformin, the clinician should note the medication dose, frequency, duration of use, remaining tablets, and last administered dose, as well as any other nephrotoxic medications. Additional questioning should include any over-the-counter medication use, supplement use, recent changes to medications, substance use history, and assessment for suicidal intent [2]. The clinician should perform a focused examination evaluating for other causes of critical illness and shock (i.e, sepsis, stroke).

Laboratory testing should include a complete blood count, comprehensive metabolic panel, venous blood gas, coagulation profile, lactate, and beta-hydroxybutyrate. Specific drug concentrations that should be considered include acetaminophen, ethanol, salicylates, metformin (if available), serum osmolality, and toxic alcohols. Additional evaluation should be tailored to the individual patient for other suspected conditions [2].

2.3. ED management

There are several components of ED management of the patient with metformin toxicity, including intravenous (IV) fluid resuscitation with balanced fluids, bicarbonate infusion in select patients, hemodialysis (HD), and treatment of any concomitant condition (e.g., antibiotics for sepsis). Activated charcoal can be considered for patients with normal mental status who present shortly after an acute ingestion. IV fluids are the mainstay of treatment for undifferentiated shock. The evidence demonstrating superiority of one isotonic solution over the other (e.g., lactated ringers [LR] versus normal saline [NS]) is limited in this patient population. However, normal saline may result in hyperchloremic metabolic acidemia, worsening the patient's acid-base status. Thus, balanced crystalloids, such as LR or PlasmaLyte, should be considered, targeting euvolemia. Bicarbonate infusion may be administered in those with severe metabolic acidemia (pH ≤ 7.0). HD is an emerging therapy that should be considered in those with lactate >20 mmol/L, serum pH ≤ 7.0, hemodynamic instability, failing standard therapies with fluids and vasopressors, and altered mental status. Emergent toxicology and nephrology consultation is also recommended. Controversial treatments include glucose, insulin, and potassium (GIK) therapy and methylene blue [3,8-10]. These should only be considered with toxicology consultation in decompensating patients and are not recommended for routine use.

Respiratory support is not typically necessary for those with metformin toxicity. However, if patients demonstrate respiratory distress, high flow nasal cannula (HFNC) may be utilized to reduce work of breathing and improve ventilatory efficiency. If intubation and mechanical ventilation are necessary, a high minute ventilation is necessary to compensate for acidosis.

3. Pearls and pitfalls

3.1. What is the difference between metformin-induced lactic acidosis, metformin-associated lactic acidosis, and metformin-unrelated lactic acidosis?

Most patients presenting with lactic acidosis in the setting of metformin use fall into one of three categories. MILA is a condition exclusively related to metformin therapy and is typically seen in renal failure patients taking metformin chronically or in metformin naive patients presenting after massive acute overdose. Plasma metformin concentrations will far exceed 5 mg/L in this condition, as elevated metformin levels are the primary cause of illness in MILA. MALA is defined as lactic acidosis in a patient with systemic life-threatening illness who is also treated with metformin. Metformin concentrations in these cases are typically >5 mg/L but lower than concentrations in MILA [2]. Though metformin partially contributes to the lactic acidosis, an alternative illness (sepsis/shock) is the primary contributor to the lactatemia. In contrast to MILA and MALA, MULA occurs in the setting of elevated lactic acid with low or therapeutic metformin concentrations (< 5 mg/L). In this setting, lactic acidosis is the product of another disease process [2].

Differentiating these entities is difficult, especially in the ED setting, where metformin concentrations are rarely processed in-house and can take several days to result. In addition, the clinical utility of a metformin concentration has not been well validated, with multiple sources noting

that metformin concentrations are not predictive of mortality [1]. Since relying on metformin concentrations is impractical in the ED setting, we advocate considering MILA, MALA, and MULA in the differential diagnosis based on risk factors in the patient's history, bearing in mind that MULA is the most common entity the emergency physician will encounter. Taking metformin therapeutically in the absence of renal insufficiency will not cause its accumulation, just as the presence of lactatemia will not cause acidemia. While the clinical rarity of true MILA and MALA should be considered, the severity of these diagnoses necessitates the physician to treat as MILA or MALA when alternative explanations of the hyperlactatemia do not fully explain that patient's clinical picture [2].

3.2. How does metformin cause a rise in lactate?

Metformin leads to a rise in lactate via several pathways. As previously mentioned, it functions as an ETC inhibitor, thus limiting ATP production to anaerobic glycolysis. A second mechanism is via its interference with the Cori cycle [11]. The Cori cycle is a process during which hepatocytes take in lactate from the tissues/muscles and oxidize lactate to pyruvate to create glucose via gluconeogenesis. Inhibition of this cycle leads to a decrease in hepatic gluconeogenesis creating an accumulation of lactate. The overall incidence of metformin causing severe lactatemia is low as compared to phenformin. This medication, now removed from the U.S. market, demonstrated a significantly higher incidence of associated hyperlactatemia (e.g., 1 in 4000 patients at therapeutic dosing with 50% mortality) [12]. Phenformin directly produces excess lactate in myocytes and disrupts the lactate to pyruvate conversion, whereas metformin does not have these actions [11].

3.3. What findings on history and examination can suggest the disease, as compared with other conditions?

History is essential in identifying and risk-stratifying patients with metformin-associated conditions. The clinician must first determine if there was an intentional overdose of metformin or if the patient is treated with metformin chronically. Patients with acute, intentional overdose ingestions have lower mortality rates compared to patients with true MALA and evidence of organ dysfunction [13]. Risk factors for MALA include alcohol use, chronic hypoxia, sepsis, advanced age, dehydration, renal dysfunction, and shock [14]. Metformin toxicity should be considered in patients taking metformin presenting with one or more of these conditions.

Certain laboratory abnormalities may portend a more complicated clinical course, including prothrombin time (PT), pH, and lactate levels. One study demonstrated that a PT value <50% of normal was associated with increased mortality [13], while another study conducted in the intensive care unit (ICU) setting demonstrated an association of mortality with abnormal PT [15]. Increased lactate concentration and decreased pH may be associated with mortality in acute metformin overdose, though this is controversial based on the quality of evidence [13,16,17]. A study consisting of patients with MALA in the ICU setting found statistically significant differences in arterial pH between those who survived and non-survivors (7.2 compared to 7.0, respectively). This study also noted a difference in lactate (11 mmol/L in survivors versus 16 mmol/L in non-survivors) [13]. Another study found acute overdose non-survivors had significantly lower median pH nadirs compared to survivors (6.71 versus 7.30, respectively) and higher peak lactate (35.0 mmol/L versus 10.8 mmol/L, respectively) [17]. Differences between studies could be attributed to a sicker patient population, type of overdose, or confounding factors with coexisting disease like sepsis or shock. Overall, the lactate concentration and blood pH should be interpreted carefully in metformin-exposed patients to avoid bias and failure to consider other causes. Elevated lactate in the setting of sepsis and other shock states is associated with increased mortality [18]. Therefore, it remains crucial to consider these patients as critically ill, maintain a wide differential diagnosis, and administer aggressive treatment (e.g., IV fluids, vasopressors, antibiotics for suspected sepsis, etc.).

3.4. What other conditions must be considered, and what conditions may result in single digit bicarbonate and double-digit lactate concentrations?

Metformin is not the only xenobiotic or disease process that can result in lactate increase (Table 1). Propylene glycol (PG) is metabolized to lactate via alcohol dehydrogenase. PG is a common excipient in many intravenous infusions such as lorazepam and used as a stabilizer in soaps and detergents. Another common group of agents producing lactatemia are the beta-2-agonists, such as albuterol. Administration of albuterol leads to excess pyruvate production which is then shunted to form lactate to resupply NAD^+ [11].

Another group of lactate-producing xenobiotics falls under the category of ETC inhibitors. This includes propofol, sodium nitroprusside, cyanide, barbiturates, and valproic acid, among others. These substances in acute overdose inhibit various complexes of the ETC, preventing mitochondrial oxidative phosphorylation and extinction of cellular respiration. Unable to efficiently generate ATP, the cell shunts energy production to anaerobic glycolysis using pyruvate as the substrate for creating lactate. One final common agent to consider is salicylates. Salicylate-containing medications and herbal formulas are readily available over the counter and frequently present in overdose. They also inhibit ETC but in a different manner. Normally, the ETC creates a hydrogen ion gradient between the matrix and intermembrane space that drives the production of ATP. Salicylates act to “uncouple” this process by allowing hydrogen ions to bypass the ETC, thus halting ATP production. The cell again reverts to anaerobic glycolysis, which results in excess lactate production [11].

While medications are a common cause of lactatemia, there is also the possibility of laboratory error and interference. The most important of these is from ethylene glycol intoxication. A noted discrepancy may occur in lactate measurements from point-of-care testing versus serum lactate testing in patients with ethylene glycol poisoning. Some point-of-care testing machines cannot differentiate the metabolites of ethylene glycol, glycolate, and glyoxalate, as they are structurally similar to lactate. Serum testing of lactate does not have this issue and oftentimes will be normal in comparison to a falsely elevated point-of-care lactate. This “lactate gap” can be diagnostic and aid in rapid identification and elimination of other medications as causes [11]. This example should draw caution to the use of the point-of-care lactate on undifferentiated patients with a higher focus on serum values.

Non-toxicologic causes of lactate must also be considered (Table 2). The most common conditions include alcoholic ketoacidosis, cardiac arrest, diabetic ketoacidosis, ischemic pathologies (e.g., limb ischemia, mesenteric ischemia), liver failure, seizures, sepsis, or starvation

Table 1
Medication/Overdose Hyperlactatemia Differential Diagnosis (list not all-encompassing).

- Acetaminophen (massive overdose)
- Barbiturates
- Beta agonists
- Carbon monoxide
- Cyanide
- Linezolid
- Lorazepam
- Metformin
- Nucleoside reverse transcription inhibitors
- Phenformin
- Propofol
- Propylene glycol
- Salicylates
- Sodium azide
- Tricyclic antidepressants
- Valproic acid

Table 2
Non-toxicologic Hyperlactatemia Differential Diagnosis (list not all-encompassing).

- Alcoholic ketoacidosis
- Cardiac arrest
- Diabetic ketoacidosis
- Inborn errors of metabolism
- Ischemia (mesenteric, limb)
- Laboratory/machine error
- Liver failure
- Renal failure
- Seizure
- Shock (adrenal insufficiency, anaphylaxis, cardiogenic, hypovolemic, sepsis, etc.)
- Starvation ketoacidosis
- Thiamine deficiency

ketoacidosis. In pediatrics, inborn errors of metabolism can result in elevated lactate.

3.5. What are the detailed components of management?

The key components of ED management include resuscitation with balanced fluids, bicarbonate infusion in select patients, and HD. Intravenous fluids are the mainstay of treatment for undifferentiated shock. The evidence demonstrating superiority of one isotonic solution over the other (e.g., LR vs NS) is limited in this patient population. We recommend targeting overall euvolemia, preferably with balanced crystalloids, and treating the underlying causes of acidosis.

The use of LR in the setting of suspected metformin toxicity or other causes of lactatemia may foster a theoretical concern that giving fluids containing *lactate* may worsen the lactemia. An understanding of sodium lactate metabolism in this context is important. Lactate is the compensatory base of lactic acid and acts as a buffer to take up a proton (H^+). While it may contribute to a modest but clinically insignificant increase in serum lactate concentration, it does not contribute to acidosis [19]. A randomized control trial (RCT) published in 2019 demonstrated a modest rise in serum lactate from a 30 mL/kg bolus of lactated ringers in healthy volunteers with no difference in lactate compared to normal saline [20]. Additionally, exogenous sodium lactate acts as a biofuel during ischemic conditions, thus limiting cell death [19].

Conversely, normal saline may result in a hyperchloremic metabolic acidosis with a theoretical risk of worsening a patient's acid base status [21]. Recent research is controversial regarding which fluid type is best in critically ill patients. An RCT of balanced fluids versus normal saline found that balanced fluids may lead to a lower rate of all-cause mortality, renal disease, and need for new HD [22]. Conversely, a more recent RCT suggested that balanced fluids were not associated with reduced mortality in critically ill patients [23].

Metformin is primarily renally cleared, so normal saline solution is theoretically a relative contraindication in metformin-toxic patients with compromised glomerular filtration rates. While it remains difficult to extrapolate results to a metformin toxic population, we suggest utilizing balanced fluids (e.g., LR, Plasmalyte) over normal saline in this patient population.

Bicarbonate infusion remains controversial in most types of metabolic acidosis given the association with increased mortality and theoretical intracellular acidosis [24]. The authors recommend consideration of bicarbonate only in cases of profound acidosis ($pH < 7.0$) as a temporizing measure to more definitive correction of acidemia using HD.

HD in this patient population is an emerging therapy. The ideal dialyzable xenobiotic has low molecular weight, low volume of distribution (≤ 1 L/kg), and low serum protein binding. Metformin is a small molecule but has a high volume of distribution with little protein binding [25], characteristics that typically make a medication a poor candidate for HD [26]. However, case reports of MALA treated with HD have been published, and a 2015 Extracorporeal Treatments in Poisoning (EXTRIP) group guideline supports HD in critically ill patients based on a review of evidence. The group concluded that metformin is "moderately dialyzable" with variability relating to the type of dialysis and the patient's renal function. The main indications for HD based on these guidelines include lactate >20 mmol/L, serum pH ≤ 7.0, and failure to improve despite standard care (e.g., IV fluid resuscitation, vasopressors). Comorbid conditions that lower the threshold for HD include shock, impaired renal function, liver failure, and decreased level of consciousness. Guidelines recommend intermittent HD with bicarbonate buffer, though continuous renal replacement therapy (CRRT) may be used if HD is not available [27].

EXTRIP recommendations are focused primarily on factors associated with increased mortality including hyperlactatemia and acidemia. These recommendations exclude pursuing metformin concentrations as their interpretation are difficult and often not readily available. When considering which patients to include in the above criteria, the focus should be on risk stratifying patients based on history, risk factors, and type of overdose rather than differentiating MALA, MILA, and MULA. Any consideration of HD should include early discussion with a nephrologist and medical toxicologist. Nephrology consult is recommended for patients with a serum $pH < 7.2$ and/or the patient who exhibits a rapid rise in lactate concentrations.

The need for respiratory support is uncommon, but if necessary, HFNC can be considered with a high flow rate (50–60 L/min) to assist with ventilation and reduce the work of breathing. If intubation is necessary, a high minute ventilation is recommended to compensate for the metabolic acidosis.

Controversial treatments include GIK therapy and methylene blue. Insulin may reduce lactate and ketoacid generation, but glucose and potassium supplementation are necessary if insulin is administered [9]. Methylene blue is another option in decompensating patients refractory to other therapies, as it may serve as a "metabolic rescue" in mitochondria, accepting electrons from NADH while transferring them to cytochrome *c*. It can also function as a vasoconstrictor [3,8,10]. Dosing is 2 mg/kg IV over 30 min, followed by 0.25 mg/kg/h IV [8]. However, as discussed previously, these are not routinely recommended and should only be administered in patients refractory to other treatments with toxicology consultation.

3.6. What mistakes are made during the initial evaluation and resuscitation?

There are several errors that may occur during the evaluation and management of the patient with metformin toxicity. There are many other conditions that may present in a similar manner with hemodynamic instability, and caution is necessary to avoid anchoring on a diagnosis of MALA in a patient treated with metformin who also has an elevated lactate. Alternative conditions such as sepsis or infarction may be present and should be treated simultaneously. Conversely, metformin toxicity should be considered a diagnosis of exclusion in critically ill patients. A thorough history and review of medications is key to avoiding these pitfalls. Additionally, when presented with a critical patient who may benefit from more aggressive therapy such as HD, consultation with the appropriate medical specialists should be accomplished early in the disease course. Lastly, adequate response to therapy should be assessed with repeat laboratory analysis at regular intervals once treatment is initiated. In patients who are not improving, treatment progression to HD may be warranted, and another condition must also be considered.

Table 3 summarizes key pearls in the evaluation and management of the patient with metformin toxicity.

Table 3
Pearls for Metformin Toxicity.

- Metformin inhibits the electron transport chain and may result in lactate production.
- Metformin toxicity exists along a spectrum and includes MULA, MALA, and MILA.
- Patients with metformin toxicity typically present with gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain) and mental status changes.
- Clinicians should review the home/outpatient medications of all patients with undifferentiated "shock" to evaluate for potential causes and concomitant conditions.
- Clinicians should consider metformin toxicity in patients with critical illness on metformin, as well as in patients who have a rising lactate level despite maximal standard medical interventions.
- Elevated lactate may be caused by a variety of conditions, including severe infection/sepsis, other toxicologic ingestion, ketoacidosis states (eg, diabetic, alcoholic, or starvation), primary medical causes, ischemia, organ failure, and/or laboratory errors.
- Management of metformin toxicity includes administration of IV fluids, treatment of concomitant conditions, and bicarbonate infusion and HD for select patients.
- Toxicology and nephrology consultation should be obtained early for consideration of HD in critically ill patients. The main indications for HD based on guidelines include lactate >20 mmol/L, serum pH ≤ 7.0, and failure to improve despite standard care. Comorbid conditions that lower the threshold for HD include shock, impaired renal function, liver failure, and decreased level of consciousness.

4. Conclusion

Metformin toxicity consists of three subgroups, including MILA, MULA, and MALA. MILA most commonly occurs in those chronically taking metformin or large acute overdoses, while MULA occurs in those on metformin but with a separate critical illness. MALA occurs with a patient on metformin who has lactic acidosis. Differentiating these entities can be challenging in the ED setting. Patients with metformin toxicity most commonly present with GI symptoms and hemodynamic instability. Laboratory analysis will demonstrate elevated lactate with anion gap metabolic acidosis. Patients presenting with elevated lactate levels in the setting of metformin use should be considered at risk for the most severe form, MALA. Treatment includes intravenous fluids, early consideration of HD, and exclusion of other causes of hyperlactatemia.

CRediT authorship contribution statement

Daniel Rivera: Validation, Visualization, Writing – original draft, Writing – review & editing. **Nancy Onisko:** Visualization, Writing – original draft, Writing – review & editing. **James Dazhe Cao:** Conceptualization, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Alex Koyfman:** Conceptualization, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Brit Long:** Conceptualization, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

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