

Delirium: A Review

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ABSTRACT: Delirium affects a diverse patient population, may present with highly variable clinical features, is a source of distress for patients and their caregivers, prolongs hospital stays and may herald a poor prognosis. Many cases of delirium are reversible and therefore a full history, physical examination and investigations should be performed. A high degree of suspicion is required for detecting delirium and thorough investigations are necessary in order to determine the underlying etiology and to maximize the potential for reversibility. The following review outlines important aspects of a clinical approach to delirium, the differential diagnosis of delirium, investigation of a patient presenting with delirium, management of delirium, the pathophysiology of delirium and the prognosis accompanying delirium.

RÉSUMÉ: Revue sur le délire. Le délire atteint différentes populations de patients et son tableau clinique peut être très varié. C'est une source de détresse pour les patients et les soignants. Sa présence peut prolonger l'hospitalisation et il peut être le signe avant-coureur d'un mauvais pronostic. Chez plusieurs le délire peut être réversible et donc une histoire médicale complète, un examen physique et des examens doivent être faits. On doit avant tout soupçonner sa présence pour le détecter et procéder à des examens minutieux pour en déterminer l'étiologie et pour maximiser le potentiel de réversibilité. Cette revue expose les grandes lignes des aspects importants d'une approche clinique du délire, son diagnostic différentiel, les examens à effectuer chez un patient qui présente un délire, le traitement, la physiopathologie et le pronostic.

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Delirium affects a diverse patient population, may present with highly variable clinical features, prolongs hospital stays and may herald a poor prognosis¹⁻⁵. Furthermore, delirium is a source of distress for patients and their caregivers⁶. Therefore, efficient detection, investigation and management of delirium are important in order to improve patient outcomes and quality of life.

The definition of delirium as per the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV-TR and DSM-V Proposed Revision) is based on the consensus of experts and enumerates four key elements: 1) a disturbance of consciousness with impaired ability to focus, sustain, or shift attention; 2) a change in cognition or the development of a perceptual disturbance that is not accounted for by a dementia; 3) the disturbance develops over a short period of time (usually hours to days) and has a fluctuating course; and 4) there is evidence based on the history, physical examination, or investigations that the cognitive disturbance is caused by a medical condition, substance intoxication, or medication side effect⁷. Delirium is not a diagnosis in itself, rather a constellation of symptoms that demands further investigation in order to determine the underlying etiology.

Differential Diagnosis and Approach to Delirium

The clinical detection of delirium can be challenging because delirium is a constellation of symptoms with a variable presentation. Three main subtypes are recognized including hyperactive, hypoactive or mixed delirium⁸. Patients with

hyperactive delirium exhibit increased motor activity, agitation, anger or euphoria⁸. Their behaviors are frequently disruptive or potentially harmful and are therefore easily identified. Moreover, there may be a clear and abrupt behavioral change⁸. Patients with hypoactive delirium exhibit decreased motor activity, anxiety, extreme fatigue, symptoms of depression or decreased motivation⁸. Patients with a mixed presentation demonstrate features of both hyper- and hypoactive delirium. The onset of delirium can be quite sudden, however, prodromal features such as mild agitation, emotional lability or increased sedation with disturbances of sleep-wake cycle may provide an early clue to the development of delirium⁸. A high index of suspicion is required, especially in cases of hypoactive delirium in which the signs of delirium are more difficult to detect.

Delirium is common in hospitalized patients, especially in elderly patients⁹, patients with chronic illness⁸, patients with advanced oncological disease¹⁰ and patients in with severe acute illnesses in the intensive care unit (ICU)¹¹. The risk for

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developing delirium is classically discussed in the context of predisposing and precipitating factors¹². Predisposing factors include intrinsic characteristics of the patient such as cognitive impairment or comorbid medical conditions. Thus, it is not surprising that patients at highest risk for developing delirium are elderly patients, patients with premorbid cognitive impairment, complex medical comorbidities, hearing or visual impairments^{1,8,13}. Precipitating factors include events that are temporally associated with the delirium including electrolyte disturbances¹⁴, medication use^{15,16}, infection^{17,18} or an acute intracerebral event among others^{1,8}.

The importance of detecting and treating delirium should be emphasized. Delirium has been associated with an increased risk of morbidity and mortality and with increased duration of hospital stay¹³. In advanced cancer and terminal illness, the onset of delirium may indicate the final stages of life¹⁹⁻²¹. In elderly patients delirium may herald the onset of early cognitive impairment^{1,22}. Furthermore, delirium is reversible in many cases and has been shown to result in psychosocial distress in recovered patients having recall of the events^{5,6}. The detection of delirium often requires a high degree of suspicion, however, multiple tools have been developed to enhance its detection (Table 1). These tools have been developed and validated for use both in general and very specific clinical situations. The current American Psychiatric Association Guideline Watch for the treatment of patients with delirium supports the use of screening tools for the detection of delirium and highlights the utility of situation specific tools such as the Confusion Assessment Method-ICU version^{23,24}. Further evidence suggests that the use of screening tools increases the detection of delirium and reduces the duration and doses used in pharmacological management²⁵.

A reversible cause for delirium should be sought in all cases. A review of the patient's past history, presenting history and medications (including recent changes) may reveal common precipitants of delirium (Table 2) such as psychoactive medications or opioid use. A complete physical examination including a thorough neurological assessment may suggest an etiology for the delirium such as infection. For clinical situations in which a clear etiology of delirium is not easily identified, basic investigations could include a chest or abdominal x-ray, urinalysis, complete blood count, electrolytes, urea, creatinine,

Table 1: Common delirium assessment tools

Common Delirium Assessment Tools
Cognitive Test for Delirium ²⁶
Confusion Assessment Method ²⁷
Confusional State Evaluation ²⁸
Delirium Observation Screening Scale ²⁹
Delirium Rating Scale ^{30,31}
Delirium Symptom Interview ³²
Intensive Care Delirium Screening Test ³³
Memorial Delirium Assessment Scale ³⁴
NEECHAM Confusion Scale ³⁵

albumin, bilirubin, aspartate transferase (AST), alkaline phosphatase (ALP), thyroid stimulating hormone and calcium, magnesium and phosphate levels^{8,11}. Pulse oximetry, urinalysis and blood cultures may be helpful. Intracranial imaging is often required and electroencephalography may be considered. Lumbar puncture is indicated for any febrile encephalopathy without other cause identified, or when meningism is detected even in the presence of other documented infections (may rule out meningitis or subarachnoid hemorrhage)⁸. A preceding history of hallucinations and behavioural change should raise the possibility of HSV encephalitis, as should the electroencephalography (EEG) finding of periodic lateralized epileptiform discharges (PLEDs). EEG will also demonstrate non-convulsive status epilepticus or patterns of cerebral activity, such as diffuse slowing or triphasic waves, that are suggestive of delirium³⁶. Further and more invasive investigations including further imaging, which may require sedation in a patient with delirium, may be indicated based on the clinical situation. The reversibility of delirium is influenced by a number of etiologic factors (Table 3) and therefore a thorough work-up is indicated^{37,38}. In the setting of advanced cancer or terminal delirium the extent of investigation may vary depending on patient and family preferences and the goals of care.

Pathophysiology of Delirium

The precise pathophysiology of delirium remains to be determined. In all likelihood, several contributors lead to the final clinical picture (Table 4). Many predisposing factors,

Table 2: An approach to the patient presenting with delirium

An Approach to the Patient Presenting with Delirium
<ul style="list-style-type: none"> □ Review of presenting history □ Medication review <ul style="list-style-type: none"> • Medications recently started • Medications recently stopped • Recent dose changes • Specific note of psychoactive medications, opioids, steroids □ Physical examination <ul style="list-style-type: none"> • Vitals • Evidence for infection • Evidence for new neurological event • Evidence for non-convulsive status epilepticus • Evaluation of pain □ Investigations – situation dependent <ul style="list-style-type: none"> • Complete blood count, electrolytes, urea, creatinine, calcium, magnesium, phosphate, albumin, bilirubin, liver enzymes, TSH • Urinalysis • Blood cultures • Pulse oximetry • Electrocardiogram • Chest x-ray, abdominal x-ray • Electroencephalography • CT brain • Cerebrospinal fluid analysis • Management – treat underlying cause <ul style="list-style-type: none"> • See table 2 • Administration of thiamine • Consider appropriateness of medical management

TSH=thyroid stimulating hormone, CT=computed tomogram

Table 3: Precipitating factors in delirium. Adapted from Moyer et al³⁸

Contributors to Delirium
Medication – polypharmacy, anticholinergic effects, psychoactive medications, opioids, steroids, antihistamines,
Dehydration
Poor glycemic control
Hypoxia
Electrolyte imbalances – hyper/hypokalemia, hyper/hyponatremia, hypercalcemia
Uncontrolled pain
Infection – respiratory, urinary
Constipation
Bowel obstruction
Organ failure – renal, hepatic, pulmonary

including pre-existing cognitive impairment, advanced age or organ failure among others, may put an individual at risk of developing delirium⁸. A leading theory regarding the pathogenesis of delirium suggests that neurotransmitter imbalances are a significant contributor to its development⁸. The neurotransmitter hypothesis proposes that dopamine excess and cholinergic deficits lead to cognitive dysfunction^{3,39,40}. The cholinergic hypothesis emerged following the observation that anticholinergic agents can be associated with delirium⁴¹. It is thought that a relative deficit of cholinergic activity contributes to the development of delirium. Studies using serum anticholinergic activity estimates, based on a receptor binding assay, have associated higher serum anticholinergic activity with more severe delirium⁴². Cholinergic imbalances can arise from exogenous medications or toxins with anticholinergic effects or from a reduction in the endogenous synthesis of acetylcholine.

The synthesis of acetylcholine depends on the presence of adequate precursors, glucose and normal function of enzymes that require thiamine for function⁵¹. Thus multiple factors

influence endogenous acetylcholine function. The cholinergic and monoaminergic neurotransmitter systems overlap both anatomically and functionally in the brain and work in concert to maintain normal cognitive function. Thus, serotonin, norepinephrine and dopamine disturbances will alter cholinergic balances and may also manifest as the syndrome of delirium. For an in depth review of the interactions between cholinergic and monoaminergic neurotransmission in the pathogenesis of delirium, see Hshieh et al⁵¹.

The inflammatory hypothesis stems from the fact that many clinical settings such as sepsis, urinary tract infection, pneumonia and post-surgical states are associated with initiation of systemic inflammatory cascades⁵². Inflammation stimulates the production and circulation of compounds including heat shock proteins, tumour necrosis factor-alpha and interleukins⁵². Emerging research supporting the inflammatory hypothesis has shown that post-operative patients have increased levels of circulating IL-6 and -8⁵³. The influence of peripherally circulating inflammatory mediators may affect the brain by

Table 4: Special considerations in delirium depending on clinical setting

Delirium Context	Consideration
Cardiac delirium	<ul style="list-style-type: none"> Heart failure may result in increased venous pressures leading to increased intracranial pressures. Cerebral hypoperfusion or hypo-oxygenation may also occur leading to impaired cognitive function and reduced level of alertness.⁴³ There is a risk of post-pump delirium following cardiac bypass surgery.⁴⁴
Hepatic delirium	<ul style="list-style-type: none"> Increases in circulating ammonia result in cerebral dysfunction. This leads to increased glutamine production by astrocytes and abnormal neuronal function.⁹
Renal delirium	<ul style="list-style-type: none"> Uremia and accumulation of other renally cleared toxins leads to cerebral dysfunction.⁴⁵
Septic delirium	<ul style="list-style-type: none"> Sepsis can alter blood-brain barrier permeability resulting in abnormal cerebral environment. Excess glutamate and oxidative stress may also play a role in the genesis of septic delirium.^{18,46}
Intensive care unit delirium	<ul style="list-style-type: none"> Generally multifactorial etiology in the ICU with multi-organ dysfunction likely playing an important role.
Elderly with delirium	<ul style="list-style-type: none"> Need to consider predisposing factors such as an underlying mild cognitive impairment or dementia.⁴⁷
Advanced cancer with delirium	<ul style="list-style-type: none"> Common contributors in advanced cancer include opioid use, electrolyte disturbances and dehydration, infections or cerebral metastases (in the case of primary non-CNS cancers). In primary CNS cancers, altered cognition and delirium may present earlier in the disease course.⁴⁸
Terminal delirium	<ul style="list-style-type: none"> Common contributors to terminal delirium are electrolyte disturbances, infection and organ failure.⁴⁹

CNS=central nervous system

Table 5: Pathophysiological theories for delirium. Adapted from van Munster et al⁵⁰

Theory	Imbalance	Comments
Neurotransmitter	<ul style="list-style-type: none"> relative dopamine excess and cholinergic deficit 	<ul style="list-style-type: none"> delirium can be induced by dopamine agonists or anticholinergics delirium may be treated with dopamine antagonists
Inflammatory	<ul style="list-style-type: none"> proinflammatory cytokines 	<ul style="list-style-type: none"> associations found between interleukin-6 and -8 and delirium in medical and surgical patients
Physiological stress	<ul style="list-style-type: none"> limbic-hypothalamic-pituitary-adrenal axis dysfunction 	
Cellular signaling	<ul style="list-style-type: none"> abnormal intraneuronal signal transduction 	<ul style="list-style-type: none"> altered neurotransmitter synthesis and release
Oxygen supply	<ul style="list-style-type: none"> decreased oxidative metabolism 	<ul style="list-style-type: none"> disturbs neurotransmitter balance resulting in cerebral dysfunction reduced cerebral perfusion during periods of delirium (APA2004)
Sleep-wake cycle	<ul style="list-style-type: none"> disturbance of sleep-wake cycle 	<ul style="list-style-type: none"> altered melatonin secretion in patents with delirium
Genetic	<ul style="list-style-type: none"> genetic predisposition may exist 	<ul style="list-style-type: none"> candidate genes include apolipoproteins, dopamine signaling

altering the activity of the hypothalamic-pituitary axis thereby altering the hormonal environment of the body and nervous system⁵⁴. For an in depth review of the neuro-inflammatory hypothesis of delirium, see Cerejeira et al⁵².

Glutamatergic and GABAergic imbalances within the thalamus are also thought to play a role³⁹. A genetic predisposition to the development of delirium may also exist and a small number of early genetic studies of delirium are underway⁵⁰. Candidate genes of interest include apolipoproteins, genes involved in dopamine transmission, interleukins, cannabinoids, acetylcholinesterases, nuclear receptors, glutamate receptors, melatonin receptors and brain-derived neurotrophic factor⁵⁰. Additional alterations in the cerebral environment likely to contribute to the genesis of delirium are outlined in Table 5. Given the wide variety of etiologic factors and clinical settings in which delirium is seen, it most likely to be the result of a multifactorial process.

In addition, pure anatomical lesions are rarely implicated in the genesis of delirium. Retrospective data suggests that acute infarction of the left (or bilateral) posterior cerebral artery territory, most specifically of the medial occipital-temporal gyri leads to confusion and delirium⁵⁵. Shih et al postulated that

infarcts in this location interrupt the inferior longitudinal fasciculus and thus interrupt neural signals between the medial temporal lobe and visual areas resulting in visually specific memory deficits⁵⁵.

Management of Delirium

Systematic review of the literature has shown that most studies investigating the prevention of delirium have been performed in surgical settings⁵⁶. A proactive geriatric consultation is of benefit in reducing the incidence and severity of delirium in hospitalized patients⁵⁶. The most important step in the management of delirium is treatment of the underlying cause. Resolution of precipitating factors can often lead to a clear sensorium. Nonpharmacological management of delirium may be initiated while the underlying cause is being investigated. Evidence suggests that reorientation using clocks, calendars, hearing and visual aids are effective interventions in delirium. A quiet and calm nocturnal environment may also help restore disturbances in sleep wake cycles^{8,57}.

In all cases, one should administer thiamine as treatment for the rare case of Wernicke's encephalopathy. Due to the variability of thiamine absorption from the gastrointestinal tract, thiamine should be administered intravenously or intramuscularly. Parenteral thiamine administration can be associated with minor adverse effects including local reactions or pruritis⁵⁸. However, reports of rare anaphylaxis reactions exist and therefore patients receiving parenteral thiamine should be monitored accordingly⁵⁸. For a more comprehensive review of Wernicke's encephalopathy and thiamine supplementation see Sechi et al⁵⁸.

Medical management of the delirious behavior is often required in order to minimize distress to the patient and family and to ensure the safety of the patient. Avoidance of psychoactive medications is preferred; however, in certain cases antipsychotic medications may be necessary in order to manage severely agitated or potentially harmful behavior⁵⁹. The most common approach includes the use of low dose scheduled antipsychotics (haloperidol 0.5-1.0 mg intravenous q12 hours (h) with dose escalation only if required). The most recent American Psychiatric Association guideline for the treatment of patients with delirium (published in 1999 with a Guideline Watch in 2004) suggests using an initial dose of 1-2 mg of iv haloperidol q2-4h prn (0.25-0.5 mg in elderly patients). The use of haloperidol is favored because it has fewer anticholinergic side effects and fewer sedating effects than other antipsychotics⁶⁰. Furthermore, haloperidol can be administered intravenously. The Cochrane Collaboration performed a systematic review of the literature on the use of antipsychotics in delirium⁵⁹. They concluded that the evidence supporting the superiority of typical antipsychotics over atypical antipsychotics in the management of delirium is not strong. In most patients the benefits of antipsychotics outweigh the risks in the medical management of delirium.

It is important to be aware of the risks associated with the use of antipsychotic medications. There is a public health advisory, released by the Food and Drug Administration (FDA), stating that chronic use of antipsychotics in the elderly may be detrimental⁶¹. The most feared result of iv haloperidol is QT prolongation (>450 msec) and the risk of arrhythmia including

ventricular fibrillation or torsades de pointes⁶². The risk may be increased in patients with a history of cardiac events, conduction abnormality or when combined with other QT prolonging medications⁶². A recent review of the literature on haloperidol and torsades de pointes showed there may be a lower risk cardiac event in patient with a normal baseline QTc, patients receiving less than 2mg cumulative haloperidol dose and patients with no other risk factors for QT prolongation⁶². In most cases, patients will only require short-term antipsychotic use. It is important to be aware of the risk for and to monitor for a prolonged QT interval and also for the risk of torsades de pointes⁶³. Meyer-Massetti et al recommend using iv haloperidol judiciously after screening for risk factors for QT prolongation and performing a baseline electrocardiogram (EKG)⁶². Continuous cardiac monitoring should be considered in patients with significant risk factors or with QTc prolongation after initiating haloperidol.

Some evidence has emerged, mostly retrospective, supporting the use of atypical antipsychotics in the management of delirium^{64,65}. Low doses of atypical antipsychotics are thought to be most effective including olanzapine (2,5-5 mg po qhs)⁶⁶, quetiapine (25-50 mg po bid)⁶⁷ and risperidone (0.25-0.5mg po bid)⁶⁸.

Other important but less frequently encountered side effects to be aware of when using antipsychotics include the risk of extrapyramidal side effects (usually dose related), neuroleptic malignant syndrome (idiosyncratic), metabolic syndrome (association with short-term antipsychotic use is uncertain) and increased mortality rates when antipsychotics are used in patients with dementia⁶⁷. Comorbidities must also be considered; for example, patients with Lewy Body dementia or Parkinson's disease are specifically at risk for the extrapyramidal side effects associated with antipsychotics⁶⁵ (quetiapine is favored in these patients).

Few trials have assessed the use of benzodiazepines in the management of delirium. Lonergan et al showed increased sedation and decreased effectiveness in treating delirium using benzodiazepines compared to antipsychotics⁶⁹ and the literature does not support the use of benzodiazepines alone⁶⁹. Furthermore, medications with anticholinergic side effects, such as scopolamine/hyoscine, dimenhydrinate, diphenhydramine or amitriptyline, may precipitate delirium in predisposed or elderly patients. In keeping with the pathophysiological theory suggesting a cholinergic deficiency, studies have also been performed investigating the use of cholinesterase inhibitors in delirium. To date, there is no strong evidence for the effectiveness of cholinesterase inhibitors in this setting⁷⁰.

New evidence has been favoring the use of dexmedetomidine as a sedative and analgesic agent for use in the intensive care unit. Dexmedetomidine is a selective alpha-2-receptor antagonist and its use has been associated with more physiologic sleep patterns, shorter duration of stay in the intensive care unit and reduced delirium^{71,72}. Studies including the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Function (MENDS)⁷³ and the Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM)⁷⁴ trials suggest that using dexmedetomidine shortens the duration of delirium and mechanical ventilation in intensive care unit patients when compared with sedation using benzodiazepines. Side effects of dexmedetomidine being investigated include bradycardia and

unexpected deaths⁷⁵. A recent systematic review by Tan et al (2010) assessing the safety of dexmedetomidine in intensive care unit patients demonstrates heterogeneity between the trials investigating its use⁷⁶. Pooled analysis of 24 randomised-controlled trials suggested a reduced duration of intensive care unit stay, without increase in the risk of bradycardia when used at lower doses. The pooled analysis did not identify an overall significant reduction in the duration of delirium⁷⁶. Further research investigating the use of dexmedetomidine in this population is needed.

In terminally ill patients, the evidence shows that chlorpromazine and haloperidol are equally effective in managing delirium in terminally ill patients with AIDS⁷⁷. The use of benzodiazepines is, once again, associated with increased sedation and there is a risk of cognitive impairment using chlorpromazine⁷⁷. Thus, haloperidol is superior in this setting, unless sedation is the desired effect. Other common interventions in terminal delirium (delirium occurring in the week prior to death⁴⁹) include supplemental oxygen or by a cool stream of room air⁷⁸, fluid and electrolyte repletion, correction of constipation or urinary retention, pain management and nonpharmacological means such as frequent reorientation and visual and hearing correction⁷⁹⁻⁸¹.

Prognosis in Delirium

The duration of delirium is difficult to predict. Elimination of precipitating factors will often improve sensorium. A recent systematic review suggests that delirium is more persistent in patients already having a diagnosis of dementia, in patients with more severe delirium as measured by clinical rating scales, or in patients presenting with hypoactive delirium⁴⁷. Patients presenting with mixed delirium are thought to have the poorest prognosis with respect to treatment response whereas patients presenting with hyperactive delirium respond more favorably to treatment⁸².

Overall, delirium has been associated with poor outcomes. In elderly patients presenting with delirium there is a risk for poor functional recovery^{2,83} and there is also a risk of subsequent cognitive decline^{1,22}. In the intensive care unit, delirium has been shown to be associated with longer length of stay both in the ICU and in hospital⁸⁴. Longer duration of delirium in ICU patients is also associated with long-term cognitive impairment following critical illness⁸⁵. In cognitively normal community dwelling individuals, the development of delirium has also been associated with a lower five year survival when compared to those without delirium⁸⁶.

Studies have shown that there is a 27% recovery in patients exhibiting terminal delirium⁸⁷. Patients with recovery from delirium had less severe symptoms and less disturbance of sleep and cognition⁸⁷. The mean time to death was almost double in terminal patients with reversible delirium as compared to irreversible delirium⁸⁷. Thus, in order to provide patients and families with the maximum possible quality time together at the end of life, active screening, detection and management of terminal delirium may be beneficial.

CONCLUSION

Delirium is frequently encountered in all areas of medicine and it appears in a diverse patient population. The clinical presentation may vary depending on the subtype (hyperactive delirium, hypoactive delirium, mixed delirium). A high degree of suspicion is required for detecting delirium and thorough investigations are required in order to determine the underlying etiology. In a majority of cases an etiology can be determined and there is the potential for reversibility. Furthermore, there is clear evidence demonstrating that delirium is associated with poor long-term outcomes. Therefore, aggressive management of agitated and potentially harmful behaviors and therapies specifically addressing the underlying cause are essential.

Summary

- A high index of suspicion is required in order to detect delirium. Clinical screening tools can assist clinicians in this process and may increase the detection of more difficult presentations including hypoactive delirium.
- Approximately 50% of delirium can be reversible. A full history, physical examination and investigations and neuroimaging should be performed in order to determine the etiology (Table 2).
- Effective management of delirium requires both nonpharmacological and pharmacological interventions. In each case, the underlying etiology must be directly addressed.
- The presence of delirium represents a poor overall prognostic factor with respect to patient outcomes (e.g. in the setting of advanced cancer delirium is associated with a higher risk of mortality).

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