The London Classification of gastrointestinal neuromuscular pathology: report on behalf of the Gastro 2009 International Working Group

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ABSTRACT

Objective Guidelines on histopathological techniques and reporting for adult and paediatric gastrointestinal neuromuscular pathology have been produced recently by an international working group (IWG). These addressed the important but relatively neglected areas of histopathological practice of the general pathologist, including suction rectal biopsy and full-thickness intestinal tissue. Recommendations were presented for the indications, safe acquisition of tissue, histological techniques, reporting and referral of such histological material.

Design Consensual processes undertaken by the IWG and following established guideline decision group methodologies.

Results and conclusion This report presents a contemporary and structured classification of gastrointestinal neuromuscular pathology based on defined histopathological criteria derived from the existing guidelines. In recognition of its origins and first presentation in London at the World Congress of Gastroenterology 2009, this has been named 'The London Classification'. The implementation of this classification should allow some diagnostic standardisation, but should necessarily be viewed as a starting point for future modification as new data become available.

Significance of this study

What is already known about this subject?

- Numerous case reports and small case series have associated gastrointestinal neuromuscular diseases with a number of underlying histopathological abnormalities.
- Recently published guidelines delineating techniques and histopathological reporting have offered some diagnostic standardisation in an area in which huge methodological variations had previously confounded the significance and reliability of reporting.
- An internationally agreed unifying classification of gastrointestinal neuromuscular pathology based on diagnostic criteria and related to clinical entities was, however, still lacking.

What are the new findings?

- The London Classification of gastrointestinal neuromuscular pathology providing a comprehensive structured system of classification based on international consensus.
- Accompanying robust diagnostic criteria for all histopathological phenotypes.
- A matrix indicating the strength of relationship between classified histopathological phenotypes and entities observed in clinical practice (on best available evidence).

INTRODUCTION

The term gastrointestinal neuromuscular disease (GINMD) describes a heterogeneous group of disorders of children and adults in which symptoms arise from neuromuscular (including interstitial cell of Cajal (ICC) or glial cell) dysfunction and interactions with other cells such as those of the immune system.[1] The symptoms of GINMD result from impaired motor activity often manifesting as abnormal transit with or without radiological evidence of transient or persistent visceral dilatation.[2] Such diagnoses include disorders limited to the gastrointestinal tract (primary) and those that are part of a systemic condition,[3] with all segments of the alimentary canal potentially affected between the oesophagus and rectum (eg, achalasia, gastroparesis, intestinal pseudo-obstruction and slow transit constipation).

METHODS

IWG participants were principally derived from adult and paediatric histopathologists and gastroenterologists with a strong interest in GINMP. A combination of 'Delphi' and 'focus group' methods were used to gain consensus, with initial in silico methods informing later face to face meetings. The number of participants (>12) and multiple rounds of written revisions fulfilled the basic criteria required for a guideline decision group[10] and allowed sufficiently reliable results at an acceptable cost, for example in terms of travel expenses. The heterogeneity of the group (speciality, nationality, expertise) was deemed desirable to be representative of a range of stakeholders. Agreement was defined without 'weighting' of any participant's views, although some participants contributed more than others to the process. All authors approved the final document. Two consensual processes were undertaken sequentially using established participatory decision-making methodology.[11]

I. Development of a comprehensive classification system of GINMP. This was based on

How might it impact on clinical practice in the foreseeable future?

- The London Classification will assist health providers in making informed decisions on the risk-benefit of full-thickness tissue biopsy and allow increased clarity of reporting and diagnostic certainty to facilitate discussion with patients regarding the nature of the disorder, prognosis and occasionally further investigation and directed treatment.
- Pathological abnormalities of the enteric neuromusculature have been demonstrated by a variety of methods for 60 years.[4] However, despite calls for standardisation dating back to the 1960s,[5] cooperative efforts to characterise and classify most gastrointestinal neuromuscular pathology (GINMP) have remained relatively neglected, with previous attempts at consensus confined to chronic intestinal pseudo-obstruction in children[6] and innervation of the colon.[7 8] In order to address these deficiencies, an international working group (IWG) was formed in spring 2007 to report to the World Congress of Gastroenterology in London in 2009 (Gastro 2009). The first aim of this group was to delineate techniques and histological reporting of GINMP. This was achieved with the recent publication of comprehensive guidelines for the handling of most specimen types from mucosal biopsies to organ resections with recommendations applicable to general pathologists.[9]
- These guidelines did not, however, produce a unifying classification with accompanying diagnostic criteria for individual histopathological conditions, nor relate such findings to observed clinical entities. A second consensual process was undertaken to address this deficiency. Here, we provide the first systematic attempt at an evidence-based classification of GINMP, which we have named 'The London Classification' in recognition of its origins and first presentation.

amalgamation and rationalisation of histopathological phenotypes agreed by the IWG during the previous consensual process,[9] and clarification of diagnostic criteria for each based on technical standards derived from the guidelines.

II. Allocation of classified histopathological phenotypes to one of two basic categories reflecting their relationship to recognised clinical entities:

Aetiological

Observed GINMP finding(s) is (are) diagnostic of a well-characterised disease with established cause and/or natural history and thus provide strong evidence of a pathogenic mechanism.

Morphological (associated) changes

Observed GINMP findings can be considered definite morphological abnormalities—that is, findings are clearly identifiable and are not seen in normal tissue, but provide only weak evidence of the pathogenic mechanism. The findings may or may not be causally related to observed clinical entities.

The scope of clinical entities was limited to chronic primary and some secondary GINMDs in which tissue is currently employed as a diagnostic adjunct (definitions included in the Supplementary material online). Diseases where dysmotility is not the central clinical characteristic (eg, Crohn's disease, radiation enteropathy and tumours of nerve, smooth muscle and ICC) were excluded.

Table 1 The London Classification of gastrointestinal neuromuscular pathology

1. Neuropathies
- 1.1 Absent neurons
  - 1.1.1 Aganglionosis*
- 1.2 Decreased numbers of neurons
  - 1.2.1 Hypoganglionosis
- 1.3 Increased numbers of neurons
  - 1.3.1 Ganglioneuromatosis†
  - 1.3.2 IND, type B‡
- 1.4 Degenerative neuropathy§
- 1.5 Inflammatory neuropathies
  - 1.5.1 Lymphocytic ganglionitis¶
  - 1.5.2 Eosinophilic ganglionitis
- 1.6 Abnormal content in neurons
  - 1.6.1 Intraneuronal nuclear inclusions
  - 1.6.2 Megamitochondria
- 1.7 Abnormal neurochemical coding**
- 1.8 Relative immaturity of neurons
- 1.9 Abnormal enteric glia
  - 1.9.1 Increased numbers of enteric glia

2. Myopathies
- 2.1 Muscularis propria malformations††
- 2.2 Muscle cell degeneration
  - 2.2.1 Degenerative leiomyopathy/‡‡
  - 2.2.2 Inflammatory leiomyopathy
    - 2.2.2.1 Lymphocytic leiomyositis
    - 2.2.2.2 Eosinophilic leiomyositis
- 2.3 Muscle hyperplasia/hypertrophy
  - 2.3.1 Muscularis mucosae hyperplasia
- 2.4 Abnormal content in myocytes
  - 2.4.1 Filament protein abnormalities
    - 2.4.1.1 Alpha-actin myopathy§§
    - 2.4.1.2 Desmin myopathy
  - 2.4.2 Inclusion bodies
    - 2.4.2.1 Polyglucosan bodies
    - 2.4.2.2 Amphophilic
    - 2.4.2.3 Megamitochondria¶¶
- 2.5 Abnormal supportive tissue
  - 2.5.1 Atrophic desmosis***

3. ICC abnormalities (enteric mesenchymopathy)
- 3.1 Abnormal ICC networks†††

*Can include rare cases of non-Hirschsprung disease severe hypoplastic hypoganglionosis with long interganglionic intervals (zonal aganglionosis).
†Although neurons have not been formally quantified, gross increases of disorganised neurons are evident.
‡Can include retarded neuronal maturation.
§May occur with or without neuronal loss but is best regarded as a separate entity.
¶May occur with neuronal degeneration and/or loss; lymphocytic epithelioganglionitis is a variant.
**Includes neurotransmitter loss (eg, reduced or absent expression) or loss of a neurochemically defined functional subset of nerves (see text).
††Includes absence, fusion or additional muscle coats.
‡‡Hollow visceral myopathy may be diagnosed in familial cases with other characteristic phenotypic features; myopathy with autophagic activity and pink blush myopathy with nuclear crowding are rare variants in which degenerative findings are less overt.
§§Smooth muscle alpha-actin deficiency is best described, although deficiencies of other proteins related to the contractile apparatus of myocytes have been reported.
¶¶Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) causes a degenerative appearance predominantly in the longitudinal muscle.
***Absent connective tissue scaffold has been almost exclusively described in the colon.
†††Generally reduced or absent ICC, although abnormal morphology also reported.
ICC, interstitial cells of Cajal; IND, intestinal neuronal dysplasia.

The decision to include or exclude other local or systemic conditions with sequelae that include neuromuscular dysfunction was based on the diagnostic utility of histopathology. On this basis several disorders have not been included at this stage. These include (1) acute conditions such as postoperative ileus and acute colonic pseudo-obstruction; (2) disease entities with established macroscopic findings, for example infantile hypertrophic

Table 2 Diagnostic criteria for histological phenotypes

Diagnosis	QL/QT	Minimum*	Adjunctive	Findings (brief)
1.1.1 Aganglionosis	QL, QT	H&E or EH	EH (AChE)	Complete absence of neurons
			IHC (calretinin)†	Hypertrophic submucosal extrinsic nerves
1.2.1 Hypoganglionosis	QL	H&E	IHC (PGP9.5, NSE)†	Severe reduction in ganglia and neurons
1.3.1 Ganglioneuromatosis	QL	H&E	IHC (PGP9.5, NSE, S100)†	Hamartomatous increase in neurons and glia
1.3.2 IND, type B	QT	EH (LDH)		>8 neurons in >20% of 25 submucosal ganglia
1.4 Degenerative neuropathy	QL	H&E		Degenerative cytological appearances
1.5 Inflammatory neuropathies	QL	H&E		Gross infiltrates or eosinophils
	QT	IHC (CD45, CD3)		≥1 intraganglionic and/or >5 periganglionic lymphocytes/ganglion
1.6. Abnormal content in neurons	QL	H&E	IHC (SUMO1), TEM	Intraneuronal nuclear inclusion bodies Megamitochondria
1.7 Abnormal neurochemical coding	QL, QT	IHC‡		Decreased immunostaining vs controls
		IHC‡	IHC (PGP9.5, NSE)† §	Reduced defined subset of neurons
1.8 Neuronal immaturity	QL	H&E	EH (LDH, SDH)	Morphologically immature neurons
1.9 Abnormal enteric glia	QL	H&E	IHC (S100, GFAP)	Marked increase
2.1 Muscularis propria malformations	QL, QT	H&E		Any departure from 2 muscle layers
2.2.1 Degenerative leiomyopathy	QL	H&E	Tinctorial¶, IHC (SMA) TEM	Myocyte damage and loss, fibrosis
2.2.2 Inflammatory leiomyopathy	QL	H&E		Inflammatory cell infiltrate
2.3.1 Muscularis mucosae hyperplasia	QL	H&E		Increased thickness muscularis mucosae
2.4.1 Filament protein abnormalities	QL	IHC (SMA)		Absent SMA in circular muscle**
2.4.2 Inclusion bodies	QL, QT	H&E		Smooth muscle amphophilic 'M' bodies
		Tinctorial (PAS)		Smooth muscle polyglucosan bodies
		TEM		Megamitochondria in myocytes
2.5.1 Atrophic desmosis	QL	Tinctorial¶		Total or focal lack of connective tissue scaffold
3.1 Abnormal ICC networks	QT	IHC (CD117) IHC (Ano1)		>50% reduced ICC in comparison with control sections

CD117 synis synonymous with c-kit; Ano1 is synonymous with DOG1.
*As recommended by IWG guidelines,[9] well-oriented sections are required at a minimum of three levels through an appropriately fixed and oriented block.
†General neural markers used for comparison (Hu C/D, neurofilament are alternatives).
‡As yet undefined—most commonly employed are: NO, ChAT, SP, VIP. Note: although provisionally included, these are not a recommendation of the international working group guidelines for general pathology practice.
§Pan-neuronal markers are used in this context to determine whether absolute numbers of neurons are reduced.
¶Trichrome, Van Gieson or picrosirius stain.
**Region specificity: this is a normal finding in ileum.
AChE, acetylcholinesteras; EH, enzyme histochemistry; ICC, interstitial cells of Cajal; GFAP, glial fibrillary acidic protein; IHC, immunohistochemistry; IND, intestinal neuronal dysplasia; LDH, lactate dehydrogenase; NSE, neuron-specific enolase; PAS, periodic acid—Schiff; PGP9.5, protein gene product 9.5; QL, qualitative; QT, quantitative; SDH, succinate dehydrogenase; SMA, smooth muscle alpha-actin; TEM, transmission electron microscopy;

pyloric stenosis, atresias, anorectal malformations and megacystis—microcolon—hypoperistalsis syndrome; and (3) other systemic diseases leading to sensorimotor dysfunction such as idiopathic autonomic neuropathy, Chagas disease, HIV and amyloid-associated neuropathy in which intestinal full-thickness biopsies are rarely undertaken.

To prevent a large number of potentially spurious or weak associations being listed, associations were limited to those in which a minimum of two peer-reviewed publications from different institutions were retrievable from the scientific literature. Key references (first and seminal where possible) that informed these relationships have been included with the results as supplementary references (S1—S130) online. Observed findings with a theoretical basis (eg, from animal studies) that could not be considered as definite pathological entities at the current time were excluded.

RESULTS

The London Classification is shown in table 1 with diagnostic criteria listed in table 2 (and Supplementary material I). Table 3 shows the provisional relationships currently ascribed by the IWG between clinical entities and histopathological phenotypes. Following several rounds of discussion, consensus was unanimous for all entries to the London Classification. Unanimity was also achieved for all relationships with clinical entities except for the placement of degenerative and inflammatory neuropathies as AETIOLOGICAL for congenital and acquired chronic intestinal pseudo-obstruction, respectively (see table footnotes for each). Adjunctive investigations which may confirm or refute such relationships are also highlighted in table 3. These include diagnoses of some primary and secondary disorders in which genetic testing might be advised for counselling, prenatal diagnosis or specific surveillance,[12 13] and diagnoses in which more complex studies may be required to clarify disease mechanism—for example, autoimmune investigation[3 14]—also prompting investigation for occult neoplasia—that is, paraneoplastic syndromes. Other specific investigations may be required for certain suspected systemic diseases, for example skeletal muscle biopsy and/or mutation analysis in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE).[15 16]

DISCUSSION

The diagnosis of GINMP requires adequate morphological study of the different components of the enteric neuromusculature and

Table 3 Relationship between clinical entities and histopathological phenotypes

	Histopathological phenotypes	
Clinical entities	**AETIOLOGICAL**	**MORPHOLOGICAL (associated) changes**
Primary disorders (References)		
Hirschsprung disease (S1–S14)	► Aganglionosis of rectosigmoid ± more proximal bowel ► Hypoganglionosis in transitional zone*	► IND type B* ► Eosinophilic ganglionitis* ► Abnormal neurochemical coding* ► Abnormal ICC networks ► Muscular hyperplasia/hypertrophy
Idiopathic achalasia (S15–S27)	► Hypoganglionosis or aganglionosis (LES) ± degenerative neuropathy± lymphocytic or eosinophilic ganglionitis± abnormal neurochemical coding (deficiency of nNOS-containing myenteric neurons)	► Abnormal ICC networks
Idiopathic gastroparesis (S28–S29)		► Abnormal neurochemical coding (loss of nNOS expression) ► Abnormal ICC networks
Congenital chronic intestinal pseudo-obstruction (S30–S49)	► Aganglionosis ► Hypoganglionosis ± intraneuronal nuclear inclusions ► Degenerative neuropathy† ► Muscularis propria malformations ► Degenerative leiomyopathy	► IND type B ► Abnormal neurochemical coding ► Neuronal immaturity ► Abnormal ICC networks
Acquired chronic intestinal pseudo-obstruction‡ (S50–S68)	► Hypoganglionosis or aganglionosis§ ± degenerative neuropathy ± lymphocytic or eosinophilic ganglionitis¶ ± Abnormal neurochemical coding (deficiency of one or more subtype of myenteric neuron) Degenerative leiomyopathy ± lymphocytic or eosinophilic leiomyositis¶	► Increased glia ► Abnormal ICC networks ► Filament protein abnormalities ► Polyglucosan inclusion bodies
Mitochondrial disorder (S69–S71)	► Megamitochondria ± abnormal cristae in ganglion cells and/or myocytes**	
Slow-transit constipation (S72–S87)		► Hypoganglionosis ± degenerative neuropathy ± Abnormal neurochemical coding (deficiency of ChAT and increase in NOS-containing myenteric neurons) ► IND type B ► Lymphocytic ganglionitis ► Abnormal neurochemical coding (other) ► Abnormal ICC networks ► Amphophilic inclusion bodies
Idiopathic megarectum/megacolon (S88–S103)		► Hypoganglionosis ± degenerative neuropathy ► IND type B ► Abnormal neurochemical coding ► Degenerative leiomyopathy ► Muscularis mucosae hypertrophy ► Filament protein abnormalities ► Atrophic desmosis
Secondary (systemic) disorders		
Muscular dystrophy (S104–S105)		► Degenerative leiomyopathy
MEN 2B (S106–S107)	► Ganglioneuromatosis	
Neurofibromatosis (S108–S110)	► Ganglioneuromatosis	
Paraneoplastic gastroenteropathy (S111–S116)	Hypoganglionosis or aganglionosis + lymphocytic ganglionitis and/or leiomyositis¶	► Increased glia
Diabetic gastroenteropathy (S117–S125)	Abnormal neurochemical coding (deficiency of nNOS-containing myenteric neurons) ► Abnormal ICC networks	► Degenerative neuropathy ► Amphophilic inclusion bodies
Connective tissue disease gastroenteropathy (S126–127)	► Degenerative leiomyopathy¶	
Cystic fibrosis (S128–S130)	► Lymphocytic ganglionitis ► Lymphocytic leiomyositis	

*May be present in the transitional zone of Hirschsprung disease and correlate with persistent obstructive symptoms if incompletely resected.
†The placement of these pathologies under AETIOLOGICAL achieved 'rough' consensus. Filamin A mutations have been identified in an X-linked form of CIPO associated with other syndromic features (short small bowel and malrotation). In these cases, grade I is clearly appropriate. However, the pathology reported (degenerative neuropathy) has not been absolutely consistent between publications, nor is it specific to the syndromic form.
‡The term enteric dysmotility encompassing patients with abnormal intestinal motor activity but without radiological evidence of obstruction, although recognised as a specific physiological entity by some experts in the field (2,20,22,24) has for now at least been amalgamated with acquired CIPO for the purposes of this classification.
§The placement of these pathologies under AETIOLOGICAL achieved 'rough' consensus. Although not all patients have an established cause or natural history, there is a rapidly increasing evidence for inflammatory neuropathies and myopathies in a proportion of patients in which inflammatory changes in the neuromuscular compartment ± circulating autoantibodies[3] may be causative. Treatment responses may be observed with immunotherapy and these findings should be reported urgently as 'critical' results.[9]
¶Histopathological diagnosis should be complemented by serum autoimmune markers (eg, antineuronal antibodies).
**This histopathological feature is not seen in all cases; definitive diagnosis typically requires other forms of testing (eg, skeletal muscle biopsy, molecular genetic analysis).
ChAT, choline acetyl transferase; CIPO, chronic intestinal pseudo-obstruction; ICC, interstitial cell of Cajal; IND, intestinal neuronal dysplasia; LES, lower oesophageal sphincter; MEN, multiple endocrine neoplasia; NOS, nitric oxide synthase.

ancillary cells. While clear abnormalities such as absence of neuronal cell bodies in ganglia or fibrosis in smooth muscle can be identified by routine histology, other lesions such as reduced or increased numbers of neuronal cell bodies require more elaborate study. The correct interpretation of pathological findings furthermore depends upon the age and sometimes sex of the patient, as well as the discrimination of artefacts from disease.[9] Previously, huge variations in methodologies and expertise have confounded the significance and reliability of a variety of reported histopathological changes in terms of clear delineation from normality.[17] The recently published IWG guidelines were designed to reduce such variability,[9] and offered a standard for acquisition and handling of tissue specimens, and interpretation of findings. This article has developed this process further by presenting a unifying classification with diagnostic criteria, and provisional relationships of such findings to observed clinical entities.

Several attempts have been made to classify clinical entities that together might be better embraced by the broad term 'gastrointestinal sensory and motor disorders' in recognition that abnormalities of either visceral sensation or contractile activity (or both) play some role in symptom pathogenesis. It is clearly beyond the remit of this article to contribute further to the debate regarding the relative validities of symptom-based (eg, Rome criteria[18]) versus measurement-based (eg, Bangkok[2]) classifications. We would, however, note that the gold standards for many common diseases are those derived from histopathology. Therefore, few would argue against a standardised form of histopathological classification for gastrointestinal neuromuscular disorders.

There is always a risk that new classification systems serve only to complicate already difficult diagnostic areas and encourage unnecessary reductionalism that may prove unhelpful in clinical practice. It could be argued that the study and classification of GINMP risks introducing a third 'blunt' diagnostic implement (the others being clinical findings and physiological testing) into the existing complex taxonomy of gastrointestinal sensory and motor disturbances. As a consequence the IWG felt it important that the London Classification be constructed around histopathological phenotypes, which are based on microscopic criteria derived from tissue handled according to 'best practice' as described in the recently published guidelines.[9] In this respect, we excluded several widely publicised pathological findings on mucosal biopsies such as mild quantitative inflammatory changes including increased intraepithelial lymphocytes or mast cells,[19 20] as the relationship between these mucosal changes and neuromuscular pathology is mostly far from clear. This decision necessarily excludes most common functional gastrointestinal disorders on the basis that suitable tissue has not been studied, even though neuromuscular abnormalities may be present, particularly in patients with 'severe irritable bowel syndrome (IBS)'.[21] Some other reported changes such as in functional subsets of neurochemically coded enteric neurons[22] and morphological changes in ICC[23] are included preliminarily, noting that in the former attribution of an aetiological role may be based on differences in methodology, i.e. some studies of achalasia and diabetic gastroparesis have conclusively demonstrated selective loss of functional subsets of neurons—for example, inhibitory (neuronal nitric oxide synthase (nNOS)+) motor neurons using overall quantitation and appropriate counterstaining—whereas others only report differences in patterns of immunostaining (which might be due to neuronal plasticity). In respect of ICC, with knowledge of a proven biological role in motility, it is tempting to attribute an aetiological role to observed changes in ICC networks. The IWG felt that this was still premature, with the exception of diabetic gastroparesis where it was deemed that sufficient experimental[24] and clinical proof exists to link these changes to the pathogenesis of delayed gastric emptying.

The proposed London Classification offers a provisional 'snapshot in time' which utilises best available evidence and coalescence of expert opinion, providing a framework that is intended to be, and should be viewed as being, open for modification in the future. Of particular relevance to future modification is the delineation of quantitative normative data for GINMP that are age, gender and region specific. The IWG identified this as the area of critical need for future research since the histopathological criteria used to define phenotypes were deliberately highly conservative based on the paucity of adequate data to provide quantitative limits of normality in the individual. Thus despite increased availability of immunohistochemical and other techniques even to the general pathologist, table 2 attests to the fact that the vast majority of diagnoses are still dependent on the qualitative examination of H&E sections. The IWG has nevertheless suggested standards that form the basis for establishment of normal values and use of more specific labelling techniques that would be applicable across centres and which are a future aim of a developing international cooperative study group.

The London Classification will assist health providers in making informed decisions on the risk-benefit of full-thickness tissue biopsy of bowel or other diagnostic procedures, even if minimally invasive.[25 26] It will also allow increased clarity of reporting and certainty of diagnosis and may thus facilitate discussion between patients and caregivers regarding the nature of a disorder and its prognosis. While the number of patients for which specific treatment can be guided by histopathology is currently limited—for example, using immunosuppressants in diseases characterised by an underlying inflammatory phenotype—further specific investigations may lead to findings such as occult malignancy.[3 22] As the classification develops further, it is envisaged that it will provide a firmer base for longer term collaborative studies with the development of databases that aim to lead to a better understanding of underlying disease mechanisms, developments in diagnostic biomarkers and perhaps more effective targeted treatments.

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