Endometritis: new time, new concepts

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Endometritis is subdivided into two categories. Acute endometritis is symptomatic and characterized by microabscess formation and neutrophil invasion in the endometrial superficial epithelium, gland lumina, and uterine cavity. Chronic endometritis is rather silent and recognized as unusual plasmacyte infiltration in the endometrial stromal areas. Over the last decade, studies have disclosed the potential association between poor reproductive outcomes and endometritis, particularly chronic endometritis. The aim of this review is to address the current literature surrounding chronic endometritis and highlight recent advances in the research of this long-neglected gynecologic disease. (Fertil Steril® 2018;110:344–50. ©2018 by American Society for Reproductive Medicine.)
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Under physiological conditions, human cycling endometrium is infiltrated by a wide variety of immunocompetent cells, including macrophages, natural killer cells, and T lymphocyte subsets. The composition and density of endometrial immunocompetent cells vary periodically across the menstrual cycle. Such timed fluctuation in local leukocyte subpopulations is thought to play a role in the tissue remodeling required to obtain endometrial receptivity (1).

Endometritis is an infectious and inflammatory disorder of the endometrium. Endometritis is histopathologically subdivided into two categories (2). One is acute endometritis, which is characterized by microabscess formation and neutrophil invasion in the endometrial superficial epithelium, gland lumina, and uterine cavity. The results of randomized controlled trials have demonstrated that acute endometritis is not associated with reduced pregnancy or elevated infertility (3). The other is chronic endometritis (CE), the histopathologic features of which are endometrial superficial edematous change, high stromal cell density, dissociated maturation between epithelium and stroma, and infiltration of endometrial stromal plasmacytes (ESPCs) (2, 4). There are currently no universally accepted standardized definitions or established diagnostic guidelines for CE, although experts agree that the presence of multiple ESPCs is the most specific and sensitive finding in this pathology (5–7).

In sharp contrast to acute endometritis being manifested with fever, pelvic pain, and vaginal discharge, the subtle and nondescript symptoms (pelvic discomfort, spotting, and leucorrhea) of CE are often unnoticed by patients and ignored by gynecologists (5). As a benign disease, interventional endometrial biopsy and arduous histopathologic examinations for CE are not favored in gynecologic practice. Accurate histopathologic diagnosis of CE has been demanding and time-consuming until recently (5). Increasing attention, however, has been focused on the potential association between poor reproductive outcomes and CE.

Here we aim to address the current literature surrounding CE and highlight recent advances in research of this long-neglected gynecologic disease. The following databases were searched for articles regarding CE until February 2018: PubMed, Embase, ScienceDirect, Wiley-Blackwell, Lippincott Williams & Wilkins, Highwire, and Google Scholar. Each database was searched using the following terms: “endometritis”, “deciduitis”, “subclinical pelvic inflammatory diseases”, and “upper female tract infection”.

MICROORGANISMS IN CHRONIC ENDOMETRITIS

The major cause of CE is microbial infection in the uterine cavity. This is supported by the fact that some antibiotic therapies are effective to eliminate ESPCs in the affected patients (8–12). The microorganisms detected frequently in endometrium with CE are common bacteria (streptococcus

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species, *Escherichia coli*, *Enterococcus faecalis*, and staphylococcus species), mycoplasma/ureaplasma species (*Mycoplasma genitalium*, *Mycoplasma hominis*, and *Ureaplasma urealyticum*), proteus species, *Klebsiella pneumoniae, Pseudomonas aeruginosa, Gardnerella vaginalis, Corynebacterium*, and yeasts (*Saccharomyces cerevisiae* and candida species) (13–15). In some developing countries, *Mycobacterium tuberculosis* is a microorganism causing chronic granulomatous endometritis, a subtype of CE characterized by poorly developed caseating granuloma and surrounding lymphocyte infiltrates including ESPCs (16).

By contrast, accumulating studies found that the detection rate of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, the principal pathogens causing acute endometritis, are very low in patients with CE (2%–7% and 0%–8%, respectively) (13, 17, 18). Moreover, administration of azithromycin or cefixime, the antibiotics targeting *C. trachomatis* and *N. gonorrhoeae*, failed to preserve future fertility in women with CE (19). *C. trachomatis* and *N. gonorrhoeae* are thereby unlikely to be the major pathogens in CE. Although their cause-effect relationship remains undetermined, such differences in the microbial profiles suggest that acute endometritis and CE are distinct pathologic entities (20).

Altered proportion in anaerobic lactobacilli species, the predominant bacteria in the female reproductive tracts (21–24), may be another characteristic of CE, although the results are conflicting between the studies. While the report employing conventional tissue culture showed a lower detection rate of lactobacilli in the endometrium of infertile women with CE than in those without CE, the others using barcoded sequencing demonstrated an increase of local lactobacilli in CE (15, 25). Further studies are required to confirm the change of lactobacilli species in the uterine cavity in CE.

A few reports implicate human immunodeficiency virus (26, 27) and cytomegalovirus (28) in CE. The association between these viral infections and CE remains uncertain.

Importantly, the microorganisms detected in the endometrial tissue are often inconsistent with those detected in the endocervical tissue or vaginal discharge (14), suggesting that the microbial examinations using lower genital tract samples cannot predict the pathogens of CE. In addition, endometrial tissue culture and conventional polymerase chain reaction were unable to identify microorganisms in more than half of infertile women with CE (15). These findings indicate the limitation of the traditional microbial examinations in the diagnosis of CE.

INFLAMMATION IN CHRONIC ENDOMETRITIS

B lymphocytes account for only less than 1% of entire leukocyte population in the nonpathological human endometrium. Endometrial B cells are mainly seen in the basal layer (the portion that persists across the menstrual cycle) as central cells in the unique lymphocyte aggregates surrounded by numerous CD8(+) T cells and macrophages (29). The role of B cells and lymphocyte aggregates in the human endometrium remains open to debate. In contrast, in CE, a large number of B cells infiltrate both the endometrial functional layer (the portion shed with the onset of menstruation) and the basal layer. These overpopulated B cells amass in the endometrial stromal compartment, trespass on the glandular epithelial areas, and invade further into the gland lumina (30, 31). Additionally, the secretory phase endometrium with CE was reported to contain a lower percentage of $CD16^{negative}$ $CD56^{positive/bright}$ natural killer cells compared with those without CE, along with an increase in T cells, indicating the aberrant mucosal leukocyte composition in this pathologic condition (32).

Several adhesion molecules and chemokines involved in B cell extravasation and migration (CD62E, CXCL1, and CXCL13) are aberrantly expressed in endometrial endothelial and epithelial cells with CE (31). The concentration of interleukin (IL)-6, a differentiation factor of mature B cells, is also markedly higher in the menstrual effluents of women with CE compared with those without CE (33). In vitro studies demonstrated that these proinflammatory molecules are induced in endometrial cells by microbial antigens such as lipopolysaccharide (31). These findings suggest that microbial infection in the uterine cavity triggers the immune responses unusual to human cycling endometrium. Such immune responses provide an abnormal microenvironment for the recruitment of circulating B cells into the endometrial stromal compartment and gravitation of these lymphocytes to the glandular areas. Furthermore, a fraction of accrued endometrial B cells may differentiate in situ into ESPCs.

Similar to other chronic inflammatory diseases, like rheumatoid arthritis and inflammatory bowel disease, the levels of IL-1β and tumor necrosis factor (TNF)-α are also elevated in the uterine cavity of CE (33). Exposure to TNF-α is known to raise estrogen biosynthesis in endometrial glandular cells (34), which may be associated with the occurrence of endometrial micropolyposis, a hysteroscopic finding that is often seen in CE (see below) (9, 35).

The ESPCs in CE legions express a high level of multiple immunoglobulin (Ig) subclasses (IgM, IgA_1, IgA_2, IgG_1, and IgG_2) with a predominance of IgG_2 (36). The excessive mucosal antibodies in CE potentially have a negative impact on the embryo implantation process. These local immune responses in CE rarely develop into systemic inflammation, as the values of the peripheral blood leukocyte counts, serum C-reactive protein, and fever index of the affected patients stay within the normal ranges (37, 38).

One of the histomorphological characteristics of CE is delayed differentiation of endometrium in the midsecretory phase. Approximately one-third of the endometrial samples with CE obtained from infertile women exhibit such "out-of-phase" morphology (37). The endometrium with CE obtained in the secretory phase often displays pseudostratification and mitotic nuclei in both glandular and surface epithelial cells. The expression of the antiapoptotic genes (*BCL2* and *BAX*), proliferation-associated nuclear marker (Ki-67), and ovarian steroid receptors (estrogen receptor-α, and -β, progesterone receptor-A, and -B) are also upregulated during the secretory phase in the endometrium with CE (39–42). By contrast, the expression of the genes potentially associated with embryo receptivity (*IL11, CCL4, IGF1*, and *CASP8*) and decidualization (*PRL* and *IGFBP1*) are downregulated in the endometrium with CE during this

period (39, 42). These findings support the idea that the endometrium with CE is unable to respond to ovarian steroids and modulate its component cells into a receptive phenotype, implicating the potential relationship between progesterone resistance and CE, as seen in endometriosis (43).

DIAGNOSIS OF CHRONIC ENDOMETRITIS

Symptomatology does not seem to help gynecologists diagnose CE, as a quarter of the affected patients lack symptoms (37). The above mentioned microbial examinations and blood tests are not instrumental. Thus, histopathologic detection of multiple ESPCs in endometrial biopsy is of primary importance in the diagnosis of CE in current clinical practice.

Be that as it may, identification of ESPCs by conventional tissue staining alone is not easy even for experienced pathologists. Plasmacytes typically have a large cell body, high nuclei/cytoplasm ratio, basophilic cytoplasm, and nuclei with heterochromatin rearrangement referred as the "spoke-wheel" or "clock-face" pattern (44). These morphological features of plasmacytes are not always evident in ESPCs under microscopic examination, as ESPCs often exhibit an appearance similar to stromal fibroblasts and mononuclear leukocytes that reside in the human endometrium. Some histological findings common in the secretory phase endometrium such as superficial edematous change and elevated stromal cell density may also interfere with the identification of ESPCs (45). Identification of glandular-stromal dyssynchrony and endometrial eosinophil infiltrates (cytoplasmic eosinophilic granules) on routine hematoxylin and eosin staining sections was proposed as a convenient screening tool to discover ESPCs but are not the absolute findings in CE (46).

Histopathologic evaluation using immunohistochemistry for plasmacyte marker CD138 (also known as syndecan-1, a transmembrane-type heparan sulfate proteoglycan) is currently the most reliable and time-saving diagnostic method for CE (47). It was shown that CD138 immunostaining is greatly superior in the detection of ESPCs to conventional tissue staining using methyl green pyronin, hematoxylin, and eosin (odds ratio, 2.8; sensitivity, 100% vs. 75%; specificity, 100% vs. 65%) with less interobserver (96% vs. 68%) and intraobserver variability (93% vs. 47%) (48–50).

Despite the usefulness of CD138 immunostaining in the diagnosis of CE, some caution should be exercised in its practical use and interpretation of results. Endometrial epithelial cells are known to constitutively express CD138 on the basolateral sides of their plasma membrane. Many of monoclonal antibodies targeting CD138 on plasmacytes are also reactive to the epitope of this antigen expressed on endometrial epithelial cells, despite that staining intensity is generally weaker than that in ESPCs (51). The conditions of the sections and immunoreactivity may occasionally cause misidentification of endometrial epithelial cells for ESPCs, resulting in potential overdiagnosis of CE. Combined use of immunohistochemistry and conventional nucleic staining is a recommended option to avoid this kind of misinterpretation.

There are currently no technical standards or conditions setting regarding CD138 immunostaining for endometrial specimens, suggesting that the diagnostic rates of CE are potentially affected by laboratory test setting and quality control including antibody selection and dilution, incubation time, thickness of endometrial sections, and number and area of sections examined (52). This problem is illustrated by a comparison of several published studies that scored inconsistent detection rates of ESPCs in cohorts of infertile women. For example, one study using a 1:1,000 dilution of clone B-B4, one of representative anti-CD138 monoclonal antibodies, showed that the prevalence of CE was 2.8% in asymptomatic infertile women undergoing their first IVF-ET cycle (52). Meanwhile, other studies using a higher concentration of anti-CD138 antibodies (1:100 dilution of B-B4 or stock solution of another frequently used clone B-A38) identified CE in 12%–30% of infertile patients (8, 31, 53, 54). Accordingly, the standardized test setting and quality control for CD138 immunostaining are indispensable to minimize the discrepancies in the diagnosis of CE.

The timing and method of endometrial sampling are also a major issue for accurate assessment of CE. ESPCs may be missed in small biopsy specimens, as these lymphoid cells often gather focally within the endometrial stroma (4, 45). In some cases of CE, ESPCs are identifiable only in the endometrial basal layer. A study using full-thickness endometrium of patients undergoing hysterectomy for benign pelvic diseases demonstrated that overlooking of ESPCs can occur more frequently in the endometrial samples obtained from surface layers during the secretory phase compared with the proliferative phase (37). Indeed, several studies showed a higher prevalence of CE in the proliferative phase than in the secretory phase (46, 55–57). Examiners should be aware of the date in the menstrual cycle and the volume of the endometrial biopsy specimens for the exact diagnosis of CE.

Finally, stringent criteria have not yet been established for the evaluation of the ESPC density in the endometrial biopsy specimen. Although the presence of multiple (two or more) ESPCs is a sine qua non for the confirmation of CE, there are some biases and variances in definitions of CE among the studies. While one study diagnosed CE with more than five CD138(+) ESPCs in at least one out of three sections levels in the endometrial biopsy specimens (47), others set the values for CE as one or more CD138(+) ESPCs in one microscopic high-power field (8). Another issue is that the endometrium of the healthy women may potentially contain some (even if only a few) ESPCs. It is crucial to redefine the minimum volumes of the endometrial samples evaluated and the cutoff density of ESPCs that is required for histopathologic diagnosis of CE.

Hysteroscopy has the potential to be a screening tool for CE. The representative hysteroscopic findings seen in CE are endometrial micropolyposis and strawberry aspects. Endometrial micropolyposis is recognized as multiple small-sized (typically 1–2 mm in diameter) protrusions arising from the endometrial surface. Endometrial micropolyposis was found in 11% of women undergoing hysteroscopy and associated with endometrial stromal edema and thickening (35). Endometrial micropolyposis is identifiable in 50%–67% of infertile women undergoing repeated implantation failure (RIF) and/or recurrent pregnancy loss (RPL) with immunohistochemically/

histopathologically confirmed CE (9, 57, 58). The etiological relationship between endometrial micropolyposis and CE remains yet to be elucidated. Meanwhile, strawberry aspects are characterized by the presence of the hyperemic endometrial areas flushed with a white central point (59). Strawberry aspects were found in 65% of women with immunohistochemically/histopathologically confirmed CE (60). There is a good positive correlation (16%–54% in sensitivity and 60%–94% in specificity) between these unique hysteroscopy findings and CE, although the studies so far suggest that hysteroscopy cannot replace the histopathologic examinations using CD138 immunostaining in the diagnosis of CE (9, 19, 60–62).

REPRODUCTIVE FAILURE AND CHRONIC ENDOMETRITIS

The reported prevalence of CE in premenopausal women ranges from 8% to 72% (5, 61). This interstudy variance is, at least in part, due to the facts that CE was investigated in a relatively small cohort (less than 100) of patients and that the conventional tissue staining was used for detection of ESPCs. Recent published data using CD138 immunostaining estimated that the overall prevalence of CE in 1,551 premenopausal women undergoing hysteroscopy and endometrial biopsy was 24.4% (57).

Several risk factors have been proposed in regard to the onset of CE. Among them is continuous use of intrauterine contraceptive devices, which is characterized by prolonged ESPC accumulation even after their removal from the uterine cavity (37, 62). Multiparity, abortion, prolonged menstruation, atypical uterine bleeding, and fallopian tube obstruction are also suggested to be the independent risk factors for CE, whereas age, obesity, oral contraceptive use, and multigravidity are unlikely (37, 62–64). Bacterial vaginosis, endometriosis, endometrial hyperplasia, submucosal fibroids, tuberculosis, and endometrial osseous metaplasia were also reported to be associated with CE (37, 65–70).

A growing body of evidence suggests a link between CE and infertility. CE is diagnosed in 28% of infertile patients with unknown etiology, 14%–41% of patients with RIF, and 8%–28% of patients with RPL (9–11, 37, 54, 57, 71). The infertile CE women with a history of RIF have a significantly lower implantation rate in the IVF-ET cycle after endometrial biopsy than those with RIF but without CE (15% vs. 46%) (8). Likewise, the per-pregnancy live birth rate in women with a history of RPL and untreated CE is very poor (7%) (10). Furthermore, women of reproductive age who contracted CE were at 60% higher risk of future infertility compared with the non-CE cohort (19).

Diffuse and extensive plasmacyte infiltration is occasionally found in the basal plate of the placenta of women undergoing obstetric complications, which is denoted as chronic deciduitis (72). Chronic deciduitis was reported to be linked to preterm labor (41%) (72, 73) and neonatal periventricular leukomalacia/cerebral palsy (20%) (74). Intriguingly, chronic deciduitis is seen more frequently in IVF-ET pregnancies resulting from donor eggs (2.8%–42%) compared with those from autologous eggs (1.6%–1.8%), suggesting that chronic deciduitis may represent chronic semiallograft rejection by the maternal immune system of the conceptus (75–77). The expression level of several proinflammatory genes (*IGJ, IGLL1, CXCL13, CD27, CXCL9, CXCL10, ICOS*, and *KLRC1)* is increased in the placenta with chronic deciduitis compared with in the placenta without inflammation (72, 78, 79). Overexpression of IgJ chain in chronic deciduitis seems to be attributable to placental infiltration of IgM and/or IgG-bearing PCs and immature B cells. An epidemiologic study supports the idea that chronic deciduitis originates in preconceptional CE rather than in ascending infection during the gestational period (74).

TREATMENT FOR CHRONIC ENDOMETRITIS

Accumulating evidence indicates the effectiveness of the oral antibiotic treatment to eliminate ESPCs in CE. A few studies reported that some progestogens (such as megestrol acetate) are another treatment option for CE, but the data are insufficient to demonstrate its effectiveness and safety (48).

Based upon its broad antibacterial spectrum covering from common bacteria to mycoplasma, doxycycline has been used as a treatment of CE (3). Johnston-MacAnanny et al. prescribed oral doxycycline (200 mg per day for 14 days) in CE patients with a history of RIF, which resulted in the clearance of CD138(+) ESPC in 70% (7/10) of the second endometrial biopsy specimens in these women. An additional treatment with a combination of ciprofloxacin and metronidazole (500 mg of each per day for 14 days) was effective to eliminate ESPCs in the remaining three patients resistant to doxycycline (8). Using the same antibiotic regimen, we prospectively investigated the effectiveness in a larger cohort of CE patients with a history of RIF (15). Oral doxycycline (200 mg per day for 14 days) alone eradicated CD138(+) ESPC in 92.3% (108/117) of CE patients and lowered the detection rate of some pathogenic microorganisms including corynebacterium, enterococcus, *E. coli, Streptococcus agalactiae, U. urealyticum*, and *Ureaplasma parvum* in the endometrium of these women, while increasing the detection rate of lactobacillus species. Moreover, the overall cure rate of CE was 99.1% (116/117 patients) following second-line treatment with metronidazole (500 mg per day for 14 days)/ciprofloxacin (400 mg per day for 14 days) for patients resistant to doxycycline.

According to the results of the endometrial microbial examinations, Cicinelli et al. classified the antibiotic regimens for the treatment of CE women with a history of RIF (11). Ciprofloxacin (1,000 mg per day for 10 days) was used for most patients who were positive for Gram-negative bacteria, whereas a combination of amoxicillin/clavulanate (2 g per day for 8 days) was given to those with Gram-positive bacteria. The patients with mycoplasm and/or ureaplasm species were treated with josamycin (2 g per day for 12 days) along with minocycline (200 mg per day for 12 days) as the second-line regimen. The patients with negative endometrial microbial examinations were administered a combination of ceftriaxone (250 mg, single dose, IM injection), doxycycline (200 mg per day for 14 days), and metronidazole (1,000 mg per day for 14 days). In this retrospective study, 28% (17/

61) of the patients overcame CE with a single course of antibiotic regimen, whereas 23% (14/61) and 25% (15/61) required the second course and the third course of antibiotic treatment, respectively. The remaining 25% (15/61) were resistant to three-time repetition of the same regimen.

McQueen et al. (10) treated infertile CE women with a history of early RPL and/or fetal demise. The first-line combination of ofloxacin (800 mg per day for 14 days) and metronidazole (1,000 mg per day for 14 days) was effective for 73% (19/26) of patients. All of the remaining nine patients resistant to this combination were cured with the second-line regimens using doxycycline alone, doxycycline and metronidazole, or metronidazole and ciprofloxacin.

For infertile women with chronic granulomatous endometritis, antitubercular chemotherapy including isoniazid (300 mg per day), rifampicin (450–600 mg per day), ethambutol (800–1,200 mg per day), and pyrazinamide (1,200–1,500 mg per day) was shown to be effective (69).

PREGNANCY OUTCOME AFTER ANTIBIOTIC TREATMENT FOR CHRONIC ENDOMETRITIS

Some studies suggest that oral antibiotic treatment potentially improves the pregnancy outcome in infertile women with CE.

In their retrospective analysis, Cicinelli et al. investigated pregnancy outcomes after antibiotic treatment in CE patients with a history of RIF (11). In the subsequent fresh day 3 ET cycle, the live birth rate (60.9%, 28/46 vs. 13.3%, 2/15) was higher in the cured CE group than in the persistent CE group. No difference was found in the live birth rate between the patients undergoing single course antibiotic treatment and those undergoing multiple course antibiotic treatment. Cicinelli et al. recently reported similar results in 95 infertile CE women with unexplained etiology (71). The cumulative live birth rate per patient after spontaneous conception in the course of a12-month follow-up was higher in the cured CE group (65.8%, 25/38) than in the persistent CE group (6.6%, 1/15) and non-CE group (4.8%, 2/42).

In a before and after study, McQueen et al. showed that antibiotic treatment increased the per-pregnancy live birth rate in CE women with a history of RPL (7% [7/98] before vs. 56% [28/50] after treatment). The cumulative live birth rate in the RPL/cured CE group was 88% (21/24), whereas that in the RPL/non-CE group was 74% (180/244) (12).

We prospectively followed up the pregnancy outcome in 118 CE women with a history of RIF undergoing antibiotic treatment (15). All of the patients had the subsequent fresh or cryopreserved-thawed cleavage-stage embryo/blastocyst transfer cycle after the second endometrial biopsy to confirm the clearance of ESPCs. The live birth rate per patient in the cured CE group after antibiotic treatment was 32.8% (38/116) in the first ET cycle and 38.8% (45/116) in three cumulative ET cycles, whereas one patient with persistent CE failed to conceive. The effect of the antibiotic treatment was notable in the cryopreserved-thawed blastocyst transfer cycles (15). The live birth rate in the cured CE group was higher than that in the RIF/non-CE group (22.1%, 50/226 in the first ET cycle and 27.9%, 63/226 in the cumulative three ET cycles), suggesting that the effectiveness of the antibiotic treatment for CE is independent of endometrial scratching effect (80).

In infertile women with tuberculosis-associated CE, antitubercular chemotherapy based on a positive endometrial biopsy–polymerase chain reaction test improved their reproductive outcomes (69). After 6-month administration of the antitubercular agents, the clinical pregnancy rate within 12 months was about 90%.

These findings support the idea that antibiotic treatment is a promising therapeutic option to improve the pregnancy outcome in infertile women with CE. Prospective randomized controlled trials are required to verify these results.

CONCLUSION

The impact of endometritis, particularly of CE, on human pregnancy has been extensively researched over the last decade, and the potential association is becoming more apparent. However, clinical evidence is still scarce about the causality between endometritis and reproductive failure including RIF, RPL, and obstetric complications. The introduction of molecular microbial technology (i.e., microbiome) into clinical practice is being actively carried out. Recent comprehensive microbial analysis based on next-generation sequencing of the 16S ribosomal subunit and/or focused real time polymerase chain reaction was shown to be a fast and inexpensive tool that can allow for the identification of both culturable and nonculturable pathogenic microorganisms associated with CE (22, 81, 82). These new approaches have the potential to shed light on the relationship between endometritis and unknown infectious conditions in the uterine cavity.

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