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Chinese expert consensus on clinical drug prevention and treatment of osteonecrosis of the femoral head （2023）

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Abstract

The in-depth understanding of osteonecrosis of the femoral head (ONFH), has lead more and more patients to seek for medical treatment in the early stage of the disease. Surgical treatment of femoral head necrosis alone is no longer sufficient for the current patients' demand. The rational and effective use of drugs to strengthen the prevention and early treatment of femoral head necrosis delaying the progression of the disease, is becoming more and more important. This article combines the latest expert consensus and evidence-based medical research on the principles of ONFH diagnosis and treatment according to Chinese and Western medicine and is organized by Chinese experts from the Association Related to Osseous Circulation and the Chinese Microcirculation Society (CSM-ARCO). This consensus was formulated with focus on drug types, characteristics, and safety. Rationality and consideration of basic principles of drug use will provide safe, reasonable, standardized, and effective drug use in medical institutions at all levels. This consensus is only an expert guideline based on literature and clinical experience, not a requirement for mandatory implementation. The clinical practice can be tailored to the actual local conditions to develop appropriate prevention and treatment measures for patients.

Keywords: Osteonecrosis of the femoral head; Expert consensus; Drug prevention and treatment

Introduction

Necrosis of the femoral head, also known as ischemic necrosis of the femoral head (osteonecrosis of the femoral head, ONFH), is a series of complex pathological processes due to the interruption of blood circulation to the femoral head, leading to the death of active cells and the subsequent repair. This condition is due to a variety of reasons (mechanical, biological, etc.) [1]. The age of onset of ONFH in China is concentrated between 40 to 50 years old [2], being predominant in male patients.

The etiology of ONFH is classified into traumatic and non-traumatic. Hormonal diseases represent more than half of the etiological causes of non-traumatic femoral head necrosis [2, 3]. Other etiologies include alcoholism, idiopathic, etc. Patients with a history of hip trauma, high-dose and prolonged application of glucocorticoids, prolonged and heavy alcohol consumption, hypercoagulable and hypofibrinolytic tendency, and autoimmune disease with use of glucocorticoids and those working in a decompression chamber are listed as the high-risk groups [4]. Smoking and obesity increase the risk of ONFH, and it was clearly determined that these factors are associated with ONFH [5].

1. Overview of the pathology and prevention of osteonecrosis of the femoral head

The pathology of ONFH is characterized by osteocyte death following microcirculatory disorders in the femoral head, subsequently granulation tissue grows-in to repair. Osteonecrosis and granulation repair often occur simultaneously. If the repair ability is strong, the femoral head can be repaired at the early stage of necrosis; if the repair ability is weak, the weight-bearing area of the hip joint will collapse and in the late-stage, osteoarthritis will follow. A typical section of femoral head necrosis is roughly divided into the articular cartilage layer, subchondral bone layer (which can be compressed by osteonecrosis), necrotic tissue layer, granulation tissue layer, neoplastic bone tissue layer and normal bone tissue layer from the outside to the inside [6].

ONFH may have no clinical symptoms in the early stage and is often detected by X-ray or MRI.

In symptomatic patients, arthralgia is mostly predominant in the groin, hip and thigh areas, occasionally accompanied by knee pain. The pain is intermittent and gradually aggravated and may be alternating if the lesion is bilateral. Other typical signs of ONFH are deep pressure pain in the groin area, which may radiate to the buttocks or knees, and a

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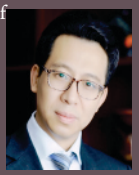
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positive "4" test. Physical examination may also include tenderness of the adductor muscles and limitation of hip joint movement, including limitation of internal rotation, flexion, and external rotation.

X-ray examination is generally taken in orthostatic and frog position which is an important basis for the imaging diagnosis of ONFH. CT examination can detect early subtle bone changes, determine the presence of femoral head collapse, as well as clarify the scope of ONFH. MRI examination is an effective non-invasive early diagnostic method and is also the gold standard. The MRI examination has high sensitivity for ONFH, which is manifested as limited cartilage-like low signal in T1WI or "double line sign" in T2WI [5].

The diagnosis of ONFH mainly relies on clinical manifestations and MRI [5]. Changes in X-ray and CT examination, can also be used as a reference basis for confirming the diagnosis. X-rays, CT examination and MRI examination, are useful for ONFH staging and typing, providing support for the selection of subsequent treatment programs.

There are many treatment methods for ONFH with different levels of efficacy. Individualized choice must be made. The general treatment goals are to delay the disease process, prevent collapse in the pre-collapse period, improving the bone quality in the peri-collapse period, and prevention of further collapse. If collapse is serious, then the treatment of joint replacement can be carried out. The treatment of ONFH can be divided into three parts, i.e., non-surgical treatment, hip-preserving surgical treatment, and arthroplasty. The choice of treatment plan should be individualized according to the patient's lesion, stage, type, considering patient's age, occupation, compliance, hospital conditions and physician's skills.

Many guidelines and expert consensus on ONFH have been proposed in recent years, including Expert Consensus on Diagnostic and Treatment Criteria for Adult Necrosis of the Femoral Head (2012 edition) [7], Clinical Diagnostic and Treatment Specifications for Necrosis of the Femoral Head (2015 edition) [4], Clinical Diagnostic and Treatment Guidelines for Adults with Necrosis of the Femoral Head (2016) [8], and Clinical Diagnostic and Treatment Guidelines for Adults with Necrosis of the Femoral Head (2020) in China [5], but all of these expert consensus lack a systematic consideration of ONFH drug therapy. Based on this, the Association Related to Circulation Osseous Microcirculation Microcirculation Society (CSM-ARCO) organized an expert group to review relevant literature at home and abroad, combined with the actual clinical experience in China, and prepared the Expert Consensus on Clinical Drug Prevention and Treatment of Necrosis of the Femoral Head. The main goal was to create a guide for clinical use of therapeutic drugs in a safe, effective, standardized, and economical manner.

2. Clinical value of drug prevention and treatment of osteonecrosis of the femoral head

At present, there is no specific drug for preventing and controlling ONFH, but after certain basic research and clinical practice exploration, scholars have found that some drugs can prevent the occurrence, reduce the development and improve the prognosis of ONFH. Their effect is more effective when applied in stages. Early ONFH includes Association Research Circulation Osseous (ARCO) stage I, II or IIIa, especially stage I and II cases, currently, the patient MRI examination has abnormalities, but subchondral fractures have not yet appeared, nor necrotic areas or femoral head articular surface flattening. Stage I cases is the golden period for drug treatment, as the sclerotic band is not yet formed as a "block".

If the treatment is appropriate, it promotes the repair of the osteonecrotic lesions, the disease process can be effectively controlled and the progression of the femoral head injury can be prevented and controlled. In some cases, even the collapse of the femoral head can be prevented and controlled.

Unfortunately, many patients consult doctors at advanced stages, and the only choice is surgical treatment. With the development of MRI technology and early screening of ONFH, more and more patients with ONFH are diagnosed at the early stage of the disease, and drug therapy has been increasing its status in the overall treatment of ONFH. Pharmacotherapy has the advantages of simplicity and ease of implementation, reliable efficacy, and good compliance. Currently, ONFH drug therapy is adopted as an individualized treatment plan, this requires clinicians to fully understand the patient's pathogenesis, disease progression, the pharmacological mechanism of therapeutic drugs, indications, and possible adverse reactions. Combination of Western and Chinese medicine is important to make different drugs work together and synergize their effects.

However, at present, incorrect, and irrational use of drugs in the treatment of ONFH occurs repeatedly, which on the one hand will affect the treatment of the disease and cause a waste of pharmaceutical resources; on the other hand, it increases the incidence of drug-induced diseases, and even the occurrence of medical adverse events. So far, there is no relevant consensus specifically for the rational use of medication in ONFH. Therefore, guiding ONFH patients to use drugs rationally is one of the urgent clinical problems to be solved.

3. Types, properties, and safety of drugs for osteonecrosis of the femoral head

Drug therapy can be applied alone or with hip preservation surgery. The drug treatment of ONFH is mainly divided into western medicine and traditional Chinese medicine. Western medicine includes anticoagulants, antiplatelets, vasodilators and lipid-lowering drugs in combination, and can also be used in combination with osteoclasts inhibitors and osteogenic drugs.

On the other hand, Chinese medicine is guided by the holistic view of traditional Chinese medicine, following the basic principles of "combination of motion and static, tendon and bone, internal and external treatment, and cooperation between doctors and patients". It emphasis early diagnosis and early treatment, striving to restore or maintain the local as well as overall stability of the hip joint [5].

Western medicine

Anticoagulants, antiplatelets, vasodilators

Currently, the pathogenesis of ONFH mainly includes mechanical causes, thromboembolism, and extravascular compression [1]. The main pathogenesis of nontraumatic ONFH is thromboembolism, so it is hypothesized that such medications can reduce the formation of femoral head microthrombi, decrease the intraosseous venous pressure, improve the circulation near

the femoral head, reverse the hypoxia, and lessen the death of osteoblasts promoting bone healing and bone repair [10]. Guo et al [11] showed that anticoagulants have a positive therapeutic effect on primary femoral head necrosis. Liu et al [12] also showed that anticoagulants and vasodilator drugs can prevent osteonecrosis induced by glucocorticoids in the femoral head and reduce the progression of the disease improving the quality of life. Albers et al [13] demonstrated a positive therapeutic effect of acetylsalicylates that have both anti-inflammatory and antithrombotic effects delaying early ONFH disease progression. Meanwhile, Cao et al [14] concluded that hip-preserving drugs can only be individualized for specific etiologies. Mont et al [15] presented a different viewpoint, suggesting that nonsurgical treatments are usually ineffective in halting the progression of non-traumatic femoral head necrosis.

(1) Indications. Early-stage patients with ONFH, especially with thromboembolic factors.

(2) Contraindications. Organ injury with risk of bleeding; hypersensitivity to heparin, low molecular heparin and their derivatives; patients with a history of thrombocytopenia associated with the use of low molecular heparin; postpartum hemorrhage and severe hepatic and renal insufficiency; severe hypertension, patients with severe craniocerebral injury and patients with acute infective endocarditis.

(3) Classification. ①Anticoagulants Anticoagulants have the best therapeutic effect on patients with early non-traumatic ONFH, especially on femoral microcirculatory disorders caused by thromboembolism. Currently, heparin analogs, such as low molecular heparin and enoxaparin, are commonly used in the clinical practice [10]; other options are vitamin K antagonist analogs, such as warfarin and bicoumarin [16]. ②Antiplatelet agents Currently, the class of cyclooxygenase (COX) inhibitors, such as aspirin, are commonly used, which have relatively few side effects through their anticoagulant effects and protection of the vascular endothelium, improving the disease progression [17]. ③Vasodilators: Vasodilator drugs can promote revascularization, and at the same time can reduce hip pain and bone marrow edema in patients with ONFH. Currently, the commonly used ones in the clinic are prostaglandin, and iloprost [18].

Inhibition of osteoclasts and increase of osteogenic drugs.

Early pathological changes of ONFH show active osteoclasts, bone resorption and destruction of bone trabeculae, which are often accompanied by focal osteoporosis due to serious loss of calcium or minerals. Irreversible collapse of the femoral head occurs in the late stage of ONFH. To slow down this process, drugs that inhibit osteoclasts and increase osteogenesis are particularly important. The commonly used clinical drugs are bisphosphonates [19], such as alendronate, which has a strong affinity for hydroxyapatite in the bone, inhibits osteoclast activity, and indirectly acts as an inhibitor of bone resorption through osteoblasts. It is characterized by strong anti-bone resorption activity without bone mineralization inhibition. Appropriate doses of active vitamin D and its analogs such as Osteotriol promote bone formation and mineralization and inhibit bone resorption. Hong et al [20] showed that alendronate was effective in delaying femoral head collapse and had positive short- and medium-term efficacy in improving joint function and alleviating hip pain. Ramachandran et al [21] found that bisphosphonates were effective in the treatment of traumatic osteonecrosis of the femoral head in adolescents and may play an adjunctive role. However, some studies have shown no statistically significant improvement in patients with ONFH treated with bisphosphonates and therefore only limited use can be recommended [22].

(1) Indications. It is indicated for patients with ONFH accompanied by localized osteoporosis or bone loss and can also be used as an adjunct in the prevention and treatment of femoral head collapse.

(2) Contraindications. Oral bisphosphonates may have adverse reactions such as esophagitis, esophageal ulcers and esophageal erosion, and rare esophageal stenosis; in addition, it is contraindicated for people with renal impairment and patients with osteochondrosis; it is contraindicated for pregnant women, breastfeeding women, adolescent children, and people with hypocalcemia and allergy to this product. Patients with long-term application of active vitamin D should be tested for blood and urine calcium levels.

Lipid-lowering drugs

The serum lipocalin levels of ONFH patients are lower than those of healthy individuals, which leads to increased bone resorption by osteoclasts, weakened osteoblast activity, and weakened mineralized bone matrix thus reducing bone mass [23]. Statin lipid-lowering drugs can elevate lipocalin levels, inhibit osteoclast activity, increase osteoblast activity, and slow the progression of ONFH. Pritchett et al [24] concluded that statin therapy reduces the risk of osteonecrosis in patients receiving hormone therapy. Clinical trials of statins alone in the treatment of ONFH are few and need to be further explored in the future.

(1) Indications. For ONFH patients receiving systemic steroid therapy and ONFH patients with concomitant hyperlipidemia [25].

(2) Contraindications. Those who are allergic to statins; patients with active liver disease; patients with severe renal impairment; patients with myopathy; patients with concomitant use of cyclosporine; women during pregnancy, breastfeeding, and women who are at risk of pregnancy and are not using adequate contraception.

Traditional Chinese medicine

Traditional Chinese medicine (TCM) can be used throughout the entire treatment process of ONFH, and should follow the principle of diagnosis and treatment, according to the patient's physique and the stage of the disease, differentiate between deficiency, solidity, cold and heat, and flexibly apply the treatment principles of benefiting qi and strengthening the spleen, promoting qi and expelling phlegm, activating blood circulation and removing blood stasis, tonifying the liver and kidneys, and transporting the heart and kidneys to select the prescription of selected medicines, and the matching of the treatment. Li et al [26] showed that the Xian Ling Bone Bo Capsule could effectively prevent the long-term application of hormone-induced femoral head necrosis in patients with immune-inflammatory diseases. Huang et al [27] also found that the Chinese herbal medicine Huo-Gu formula (HGF) showed beneficial effects

in preventing femoral head collapse, delaying total hip arthroplasty, and maintaining physical function in hormone-related ONFH treatment.

Bone morphogenetic protein (BMP) therapy

BMP can directly induce osteogenesis and can also induce angiogenesis at the site of osteonecrosis by affecting the expression of vascular endothelial growth factor (VEGF), which in turn promotes osteogenesis [28]. The recombinant human bone morphogenetic protein-2 (rhBMP-2) has been used in clinical research. Sun et al [29] concluded that rhBMP-2 may improve the clinical efficacy and quality of bone repair, and that this treatment regimen is more effective in patients with C and L1 types in ARCO stage II or China-Japan Friendship Hospital (CJFH) staging. Animal studies have shown that the combination of bisphosphonates can be better [30], but further clinical studies are needed in the future.

Stem cell therapy

Stem cell therapy is often used in combination with core decompression. The addition of bone marrow aspirate concentrate (BMAC) can increase the local bone mass in the necrotic area of the femoral head [31]. Mesenchymal stem cells (MSCs) are commonly used [32], which can differentiate into osteoblastic cells [33], but further clinical research is needed. MSCs can differentiate into osteoblasts and vascular endothelial cells, generating osteo-angiogenic coupling mechanisms [33], and can also produce growth factors through paracrine effects to promote the repair of necrotic areas circulation [34,35]. Mao et al [36] concluded that the use of medullary core decompression in combination with stem cell therapy can effectively alleviate the ONFH in young patients (less than 40 years old) who have not yet collapsed their femoral head [37].

Platelet-rich plasma (PRP) therapy

PRP therapy is often used in combination with core decompression to induce angiogenesis and osteogenesis, thereby accelerating bone healing, inhibiting inflammation in necrotic lesions, and preventing glucocorticoid-induced apoptosis of osteoblasts. Han et al [37] concluded that PRP, as an adjunctive therapy to core decompression, improved the treatment of patients with early stage ONFH by inducing osteoactivation and stimulating stem cell differentiation in necrotic lesions, and was more effective when used in combination with stem cells and bone grafts.

Rationality and basic principles of medication for osteonecrosis of the femoral head

The purpose of ONFH drug therapy is to reduce or eliminate pain and discomfort, improve microcirculation in the femoral head, promote osteogenic repair, slow down the progress of the disease, and improve the quality of life of the patients. Most of them are mainly treated with oral anticoagulant, lipid-lowering, and Chinese and Western medicines that inhibit osteoclasticity and promote osteogenesis. Therefore, it is necessary to carry out individualized and reasonable drug treatment according to the stage of ONFH patients' condition, especially whether the femoral head collapses or not.

Reasonableness of choosing drugs in different stages

Pre-collapse of femoral head

Before the collapse of the femoral head the clinical findings are not obvious. Most of the patients only have MRI abnormalities. This is the golden time for drug treatment, anticoagulation, lipid-lowering, expanding blood vessels, inhibiting osteoclasts, and increasing osteogenesis [18]. Attention should be paid to the patient's own condition, such as high blood pressure, and blood lipids to select drugs specifically for each patient. Drugs can be combined with Chinese herbal medicine, either taken internally or externally, to tonify the liver and kidney, activate the bone, and promote the growth of the liver and kidney. In order to improve bone metabolism and relieve pain, the principle of tonifying the liver and kidney, activating blood circulation and strengthening the tendons and bones should be followed. However, if there is obvious pain in the groin area, it is mostly caused by bone marrow edema, which indicates that the femoral head necrosis area has undergone cephalic instability and is about to progress to the peri-collapse stage.

Peri-collapse stage of femoral head without total hip arthroplasty

The clinical symptoms of patients at this stage are mostly typical symptoms, and at this time, only relying on medication cannot slow down the process of the disease being the therapeutic effect poor. Therefore, hip-preserving surgery combined with drug therapy is often chosen. At this time, in addition to anticoagulation, lipid-lowering, vasodilatation, inhibition of osteoclasts, and increasing osteogenesis, other options as BMP, PRP, or stem cell therapy can be used combined with surgery. At the same time, traditional Chinese medicine treatment is also very important, with the use of blood circulation, blood stasis and collaterals, kidney and bone strengthening. Traditional Chinese medicine can improve the effect of hip preservation surgery [38].

Rationality of medication for different individuals

Combined underlying diseases.

(1) Cardiovascular and cerebrovascular diseases: The incidence of cardiovascular and cerebrovascular diseases in patients with ONFH is higher than that in the normal population [39], so clinicians need to pay attention to cardiovascular and cerebrovascular function of the patients, and if there are serious diseases and risks, they need to be careful when using drugs with great influence on this pathologies. This is especially important when using vasodilators due to their cardiovascular and cerebrovascular effects.

(2) Diabetes mellitus: Type 2 diabetes mellitus is one of the common diseases in elderly patients. In type 2 diabetes mellitus patients, insulin insufficiency can affect the formation of bone matrix and its mineralization through a variety of pathways or promote bone resorption producing osteoporosis. In addition, peripheral nerve lesions and superficial sensory loss, joint motor reflex dysregulation, joint and ligament load imbalance, can favor femoral head collapse and deformation and compression of intraosseous microvessels when weight bearing. Blood glucose levels control improves microcirculation in the femoral head.

(3) Digestive tract diseases: If severe gastrointestinal disorders and risks are

present, consultation with gastroenterology is required and drugs with high gastrointestinal effects should be used with caution. Particular attention needs to be paid to osteogenic drugs, such as bisphosphonates [40]. Its main adverse reactions are reflected in the digestive tract, so attention should be paid to monitoring the patient's digestive system symptom. Timely adjustment of drug dosage or measures to protect the digestive tract is very important.

Age: ONFH can occur in all ages. Although the main group includes middle-aged and young people, the elderly can also be involved.

Most patients do not want to go through surgery unless they have no choice. Elderly patients, with reduced organ function and more concomitant underlying diseases, will have an increased level of surgical risk. Therefore, drug therapy is becoming more and more important. In elderly patients, great care should be taken when selecting drugs. Elderly patients have more comorbidities and complex medication situation, so careful attention to the medical medical record is essential to avoid the occurrence of adverse reactions [41].

The ideal is to use the lowest doses for a limited time. The appropriate selection of the dosage taking into account the patient's risk factors minimize side effects.

Elderly people have declining liver and kidney functions and poor metabolizing ability, these should be considered to timely adjust drug dosage. On the other hand, in relatively young patients with ONFH, in which most cases are related sports trauma or are idiopathic, the treatment should aim to preserv the hip joint as much as possible [42], so early drug treatment is particularly important. If the progression of the disease cannot be effectively alleviated, the patient may face total hip arthroplasty as well as several revision surgeries, which increases the physical, mental and economic pressure on the patient.

Primary morbidity

More than half of the patients with non-traumatic ONFH have taken hormones, and among these patients, most of them have autoimmune diseases, with systemic lupus erythematosus predominating [2], in addition to renal disease, facial nerve paralysis, hematologic disorders, organ transplantation, and so on. In the therapeutic process of ONFH, the treatment of such patients is more difficult, and the dosage of hormonal drugs need to take this into account.

Precautions for the rational use of drugs

(1) When using anticoagulant and antiplatelet drugs, generally combined with vasodilator drugs, attention should be paid to the evaluation of patients' coagulation function, to prevent cardiovascular and cerebrovascular diseases. (2) All drugs should be used in strict accordance with the instructions, paying attention to whether there is a mutual reaction between different kinds of drugs. In patients with underlying diseases it is necessary to reasonable adjust the drugs doses. (3) In elderly patients, attention should pay to liver and kidney function. If abnormal liver and kidney function occurs, reducing or stopping the drug may be necessary. (4) Because of the long duration of use, adverse drug reactions caused by long-term use of drugs can appear.

Key points of the expert consensus on clinical drug prevention and treatment of osteonecrosis of the femoral head

(1) Treatment principles: ONFH should be detected early and treated early. Individualized Chinese and Western medicine should be used to improve the treatment effect.

(2) Application of drugs.

(a) Anticoagulant, antiplatelet, and vasodilator drugs can improve blood circulation in the femoral head, reverse hypoxia, reduce bone cell death, and promote bone healing.

(b) Osteogenic drugs, can promote local osteogenic repair, improve osteoporosis, delay the progress of the disease, and prevent the collapse of the femoral head.

(c) Statin lipid-lowering drugs can elevate the level of lipocalin, inhibit osteoclast activity, increase osteoblast activity, and delay the progression of ONFH.

(d) Chinese medicine treatment is based on different stages and patients' physique, based on strengthening the spleen and regulating the kidneys, supplemented by activating blood, clearing collaterals, dispelling phlegm, and inducing dampness. Individualized prevention and treatment methods are chosen according to different clinical signs and symptoms of the patients.

(e) Drugs producing anticoagulation, lipid-lowering, blood vessel expansion, inhibition of bone-breaking, and increase of osteogenesis are usually prescribed in combination to achieve better therapeutic effect.

(f) In cases of ONFH with a large extent of osteonecrosis in the peri-collapse stage or pre-collapse stage, synergistic treatment with BMP, stem cell therapy, PRP, traditional Chinese medicine and hip-preserving surgery can be used.

Conclusion

ONFH should be detected and treated early, especially when using drug treatment, which aims to improve the microcirculation of the femoral head, promote osteogenic repair, delay the progression of the disease, strengthen the bone quality, prevent the femoral head from collapsing, improve the function of the joints, and increase the quality of life of the patients. The treatment plan should be formulated based on comprehensive consideration of factors such as MRI, hemodynamic changes in femoral head necrosis, osteonecrosis staging, typing, necrosis volume, joint function, patient's age, occupation, and adherence to joint preservation therapy.

This consensus is only a guiding opinion of experts based on literature and clinical experience, and is not a mandatory requirement for implementation, let alone a legal basis. In clinical practice, prevention and treatment measures can be customized according to local conditions and tailored to the patient's needs.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Conflicts of Interest: Nil.

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