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Mini Review

Dual Effects and Clinical Application Prospects of Hyperbaric Oxygen Therapy in Glioblastoma: A Mini Review

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Abstract

Glioblastoma remains a highly challenging malignancy with a pronounced tendency for recurrence. The hypoxic microenvironment is a key contributor to its therapy resistance. Hyperbaric oxygen therapy (HBOT), which elevates tissue oxygen pressure and reverses hypoxia, exhibits a "dual effect" in glioblastoma management. This review aims to evaluate the therapeutic potential of HBOT in glioblastoma by examining its multifaceted effects on tumor biology and treatment response. On one hand, it enhances radiosensitivity through reactive oxygen species generation, increases chemotherapy efficacy by augmenting cytotoxicity and improving vascular perfusion, and remodels the tumor microenvironment via vessel normalization, edema reduction, and immune cell modulation. Furthermore, HBOT attenuates cancer stem cell properties by downregulating stemness markers and inhibiting self-renewal capacity. On the other hand, HBOT may also promote tumor progression: oxidative stress can induce genomic instability, while concomitant activation of HIF-, NF-κB-, and VEGF-mediated pro-survival pathways may facilitate malignant cell adaptation and proliferation. Given these opposing considerations, the clinical application of HBOT in glioblastoma management remains exploratory. In conclusion, future research should focus on optimizing HBOT protocols. In addition, exploring combination with other therapeutic approaches is equally important. These efforts are essential for the safe and effective integration of HBOT into comprehensive treatment strategies for glioblastoma.

Introduction

Glioblastoma is the most common brain tumor. It remains one of the most challenging malignancies in neuro-oncology due to its highly invasive, diffuse growth and resistance to conventional therapies.[1–3] Although the standard regimen, comprising surgery, radiotherapy, and temozolomide (TMZ) chemotherapy, remains the cornerstone of glioblastoma therapy, its efficacy is limited, resulting in high rates of recurrence and poor patient outcomes.[4–6] Previous research has consistently highlighted the critical role of the hypoxic microenvironment in promoting tumor progression. Hypoxia is widely prevalent within glioblastomas and serves as a key contributor to malignant progression and treatment resistance.[7,8] Hyperbaric oxygen therapy (HBOT), which involves inhaling pure oxygen at 1.5–3.0 atmospheres absolute (ATA), markedly increases oxygen pressure in tumor tissue, offering a promising approach to counteract tumor hypoxia. Consequently, its application in glioblastoma treatment has garnered widespread attention and research in recent years.[9,10] However, HBOT exhibits a complex "dual effect" in glioblastoma: it may enhance antitumor efficacy but also poses a risk of promoting tumor progression.[10,11] This review aims to evaluate the therapeutic potential of HBOT in glioblastoma by synthesizing current research evidence, elucidating its molecular mechanisms, and examining its clinical applications. In addition, it provides insights into future research directions and potential therapeutic developments.

Keywords: Glioblastoma; Hyperbaric oxygen; Hypoxic microenvironment; Radiochemotherapy sensitization; Immunity; HIF pathway; ROS; Dual effect.

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Biological basis of HBOT in glioblastoma

Disordered vasculature and high metabolic demand in glioblastoma cells lead to oxygen consumption that exceeds supply, resulting in intratumoral hypoxia.[12] Studies indicate that oxygen levels in glioblastoma tissues are generally below 5% and can fall below 0.1% in necrotic core regions, creating essentially anoxic conditions.[13] The anaerobic microenvironment has been proven to promote malignant growth, invasion, and resistance to radio-

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therapy and chemotherapy in glioblastoma.[12,14,15] For example, a 2009 study demonstrated that glioblastoma cells in low-oxygen conditions had higher levels of the stem cell marker CD133. This increase promoted malignant transformation and enhanced treatment resistance.[14] Additionally, Kolenda *et al.*[15] used an *in vitro* model to simulate hypoxia and found that hypoxic cells expressed higher levels of resistance molecules (MGMT, MRP1, MDR-1, and Lamp-1), contributing to therapy resistance and tumor growth. This finding has also been reported in other studies.[16,17] Our previous studies also showed that tumor cells in hypoxic conditions grow faster,[11,18,19] undergo less apoptosis, are more invasive, and have increased resistance to TMZ. *In vivo* studies revealed that mice under hypoxic conditions developed tumors more quickly, resisted chemotherapy, and had shorter survival rates.

HBOT is an important method for treating hypoxia.[10,11] It is mainly used for brain injuries, cerebral hemorrhage, strokes, and complications from cranial surgery.[20,21] Its use as an additional treatment for malignant glioblastoma is still being researched. Under hyperbaric conditions (typically 1.5–3.0 ATA), patients breathe 100% oxygen, which greatly increases the oxygen dissolved in plasma. This high oxygen pressure effectively reverses tissue hypoxia. While some studies have explored the application, their conclusions are inconsistent.[9–11,22,23] The dual effects of HBOT complicate its implementation in glioblastoma therapy.

Anti-tumor potential of HBOT

HBOT enhances the radiosensitivity of glioblastoma cells. Radiotherapy induces reactive oxygen species (ROS). These lead to DNA double-strand breaks, lipid peroxidation, and protein damage in tumor cells. These are key mechanisms of cell death.[24,25] HBOT can raise oxygen levels in tumors by 100–115%.[26] This boosts DNA damage from radiotherapy and improves control rates. A study in 2022 demonstrated that combining HBOT with radiotherapy resulted in significantly greater proliferation inhibition and higher apoptosis rates in U251 cells compared to radiotherapy alone.[27] Other studies have confirmed that HBOT before radiotherapy significantly suppresses glioblastoma growth, improves control, and extends survival.[9,28,29]

In addition, HBOT can improve the efficacy of chemotherapy in glioblastoma. The hypoxic tumor microenvironment impairs DNA repair, drug delivery, and cellular metabolism.[30–32] HBOT improves oxygen levels and enhances the effects of drugs like nimustine (ACNU) and TMZ.[10,11] A study in 2016 demonstrated that HBOT inhibited glioblastoma cell proliferation and enhanced ACNU's effects by raising oxygen pressure (PO_2) in tumor tissues and lowering hypoxia-inducible factor (HIF)-1α, tumor necrosis factor-α, interleukin-1β, vascular endothelial growth factor (VEGF), matrix metalloprotease 9, and nuclear factor kappaB (NF-κB).[33] Another study reported that HBOT combined with TMZ reduced intratumoral vessel density and Ki67 expression.[34] Stuhr *et al.*[35] found that hyperoxic treatment slowed tumor growth and increased apoptosis in glioblastoma xenografts. Our studies confirmed that while HBOT alone promoted glioblastoma cell proliferation by inhibiting HIF-1α and HIF-2α, combining it with TMZ led to smaller tumors and longer survival compared to chemotherapy alone.

Moreover, HBOT can also promote the effectiveness of targeted therapies in glioblastoma. Xie *et al.*[36] studied whether vitexin, an HIF-1α suppressor, could enhance HBOT-mediated radiosensitization in a xenograft model. The results showed a notable tumor size reduction when combined with HBOT, indicating that HBOT makes glioblastomas more sensitive to vitexin-enhanced radiotherapy. Similarly, Zembrzuska *et al.*[37] reported that a CK2 inhibitor combined with HBOT suppressed cell proliferation and survival, showing a promising therapeutic strategy for malignant glioblastoma.

Modulation of the tumor microenvironment and immunity

HBOT enhances radiochemotherapy sensitivity through modulation of the tumor microenvironment and immune responses (Fig. 1). It improves oxygenation, which can help partially normalize tumor blood vessels within a certain time frame. As a result, drug delivery and immune cell infiltration can increase.[38,39] Additionally, HBOT enhances drug distribution by boosting tumor blood flow, which helps with chemosensitization.[40] HBOT causes blood vessels to constrict, lowers vascular permeability, and reduces peritumoral edema. This improves clinical symptoms in patients.[41,42] These effects can create better conditions for other treatments and are a traditional benefit in the central nervous system.

HBOT also influences immune cell function. For example, it enhances macrophage phagocytic capacity and alters cytokine release (*e.g.,* increasing interleukin-10).[43] It inhibits the infiltration of inflammatory cells by suppressing tumor necrosis factor-α, NF-κB, and interleukin-1β.[33] The overall impact of HBOT on the tumor immune environment is complex, involving both anti-tumor and pro-tumor effects. More studies on specific immune cell types are needed.

In addition, glioblastoma stem cells are a primary cause of treatment resistance and recurrence, often enriched in hypoxic niches.[14] Research has found that HBOT can downregulate stemness markers (e.g., CD133, CD15, SOX2) in certain glioblastoma cells. It also inhibits their self-renewal and tumor formation *in vivo*.[10,11,28] Moreover, HBOT reduced the proportion of $CD133^{+}A2B5^{+}$ cells and stemness-related genes while increasing TGF-β and β-catenin.[22] These results suggest that HBOT may help disrupt the glioblastoma stem cell microenvironment.

Potential pro-tumorigenic risks and controversies of HBOT

Despite potential benefits, concerns remain about HBOT's risk of promoting tumor progression in oncology, especially with glioblastomas (Fig. 1). Wang *et al.*[44] reported that HBOT promoted the growth of exotransplanted GL261-Luc cells and reduced necrosis in a C57BL/6J mouse model. Ding *et al.*[45] observed larger tumor volumes in Sprague–Dawley rats with glioblastoma xenografts after HBOT. Our study confirmed that HBOT inhibited pro-apoptotic protein Bax and promoted tumor growth. These findings highlight the ongoing debate about HBOT's "dual effect".

While HBOT can enhance ROS cytotoxicity, elevated oxygen may also increase ROS-related DNA damage and epigenetic changes, leading to genomic instability. If the damage exceeds the cell's repair capacity, mutation rates might rise, potentially speeding up tumor evolution.[46] Additionally, tumor cells may activate survival pathways in response to oxidative stress. Nakajima's research showed that ROS can activate NF-κB early on,[47] amplifying cytokine-induced NF-κB activation. ROS also contribute to carcinogenesis and inflammation through various mechanisms, such as DNA damage and activation of specific kinases and transcription factors. Yamamoto *et al.*[48] found that HBOT stabilizes HIF-1α through nitric oxide signaling, increasing VEGF and basic fibroblast growth factor, laying the groundwork for angiogenesis and cell growth. In contrast, ROS or nitric oxide pathway inhibitors (N-acetylcysteine or Nω-nitro-L-arginine methyl ester) can effectively block these pro-angiogenic and pro-proliferative effects.

A key objective of HBOT is to reverse hypoxia and inhibit HIF-1α. HIF-1α is a crucial transcription factor for tumor adaptation to

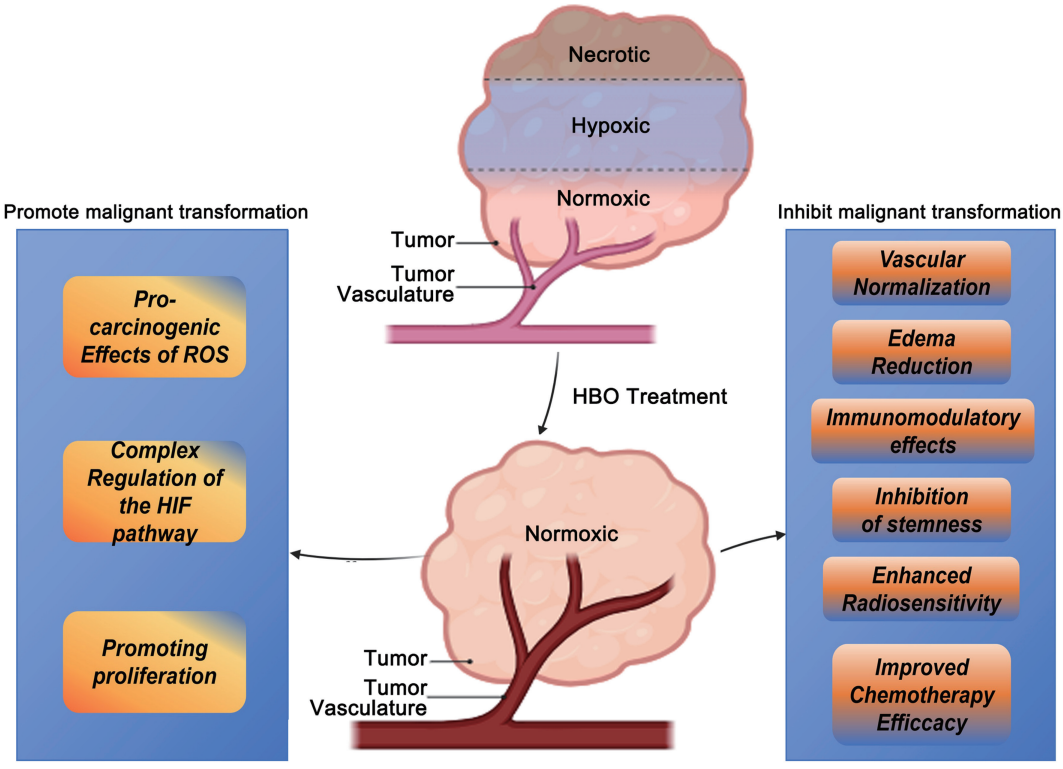

Fig. 1. Dual effects of hyperbaric oxygen treatment in glioblastoma. Hyperbaric oxygen therapy (HBOT) displays anti-tumor potential by enhancing radiosensitivity and chemotherapy efficacy while remodeling the tumor microenvironment and immune response. Conversely, it may also fuel tumor progression via reactive oxygen species (ROS) activation and pro-survival signaling pathways.

hypoxia,[48] promotion of angiogenesis,[49,50] metabolic reprogramming (e.g., glycolysis),[51,52] and invasion and metastasis.[53,54] Effective inhibition of HIF-1α is a desired anti-tumor effect. However, HBOT may induce intermittent hypoxia–reoxygenation, which itself can strongly induce oxidative stress and activate various stress signaling pathways, including HIF-1α.[48] Furthermore, ROS can stabilize or activate HIF under specific conditions.[48,53] Thus, HBOT's overall effect on the HIF pathway, whether it inhibits or activates, depends on treatment factors like pressure, duration, and frequency, as well as the specific tumor context. This dependency is crucial for understanding its dual effect.

Clinical research of HBOT on glioblastoma and the application scenarios

The clinical use of HBOT in glioblastoma remains exploratory, mainly as an adjuvant to standard therapies. To establish HBOT as a reliable component of glioblastoma management, current challenges must be addressed.

Treatment of radiation necrosis (RN) and postoperative recovery is the most established application of HBOT in neuro-oncology. RN, characterized by refractory edema, neurological deficits, and mass effect, can occur after radiotherapy. Multiple studies support HBOT's effectiveness in reducing edema, repairing necrotic tissue, and improving neurological symptoms in RN.[55,56] Some studies have explored its practical application in the early postoperative period to reduce peritumoral edema, improve wound healing, and alleviate neurological deficits.[26,57] However, its precise value relative to conventional treatments (e.g., corticosteroids) still requires evaluation. For severe cerebral edema, HBOT may serve as an auxiliary option.

Besides, clinical trials are investigating the use of HBOT (typically at 1.5–2.0 ATA) along with radiochemotherapy (with or without TMZ) to improve efficacy and oxygenation. Some small-scale clinical studies suggest that combining therapies may prolong progression-free survival and even overall survival, though results are inconsistent and large trials are needed.[58] Tanaka *et al.*[59] studied 11 patients with recurrent glioblastoma; all received cisplatin, and some received additional HBOT. Significant differences in survival curves were observed between the two groups. Due to the small sample size, Suzuki *et al.*[60] recruited 129 patients in 2009, finding that the HBOT-plus-cisplatin group had a median survival of 768.2 days versus 591.2 days for cisplatin alone, indicating HBOT as a favorable factor. In 2012, Ogawa *et al.*[23] treated 57 high-grade glioblastoma patients with HBOT followed by radiotherapy and PCV chemotherapy, reporting longer median survival than historical controls. Kohshi *et al.*[61] noted better tumor regression and median survival in patients receiving HBOT with radiotherapy. Collectively, these studies suggest that HBOT may improve outcomes such as survival and response rates when combined with radiochemotherapy.[57,62]

Future therapeutic strategies

A review of existing literature shows that researchers typically used only one set of parameters for hyperbaric oxygen treatment, without categorizing patients into subgroups. Additionally, combination therapies have mostly been limited to traditional radiotherapy and chemotherapy (Table 1).[5,10,11,22,23,27,28,34,36,37,41,44,45,60,61] Conse-

Table 1. Summary of studies of HBOT in glioblastoma

Authors	Year	Oxygen pressure/Time	Study/clinical study	Outcome
Arienti *et al*.[5]	2021	1.9 and 2.5 ATA, 60 min	Primary GBM cells	HBOT attenuates the malignant phenotype of glioblastoma through metabolic intervention
Gong *et al*.[10]	2025	2.5 ATA, 90 min	U87, A172 cells and GBM	Combined treatment with HBOT and TMZ significantly suppresses malignant progression in glioma
Wang *et al*.[11]	2021	2.5 ATA, 90 min	Primary GBM cells from 3 different patients	HBOT promoted both proliferation and chemosensitization of glioblastoma cells
Song *et al*.[22]	2020	3 ATA, 60 min	Basal ganglia glioma rat model	HBOT can change the hypoxic micro-environment and affect the stemness-associated characteristics of cancer cells
Ogawa *et al*.[23]	2012	–	57 patients with malignant glioma	Radiotherapy delivered immediately after HBOT with multiagent chemotherapy was safe, with virtually no late toxicities, and seemed to be effective in patients with high-grade gliomas
Ma *et al*.[27]	2022	–	U251 glioma cells	HBOT can enhance the proliferation inhibition and apoptosis of glioma U251 cells and improve the radiosensitivity of U251 glioma cells
Yuen *et al*.[28]	2023	1.5 ATA, 90 min	T98G glioma cells and Primary GBM cells	HBOT shows promise as an adjuvant treatment for GBM by reducing cancer stem cell formation and enhancing sensitivity to chemotherapy and radiotherapy
Lu *et al*.[34]	2016	2.5 ATA, 90 min	nude mice expressing EGFP, SU3 human glioma cells	HBOT can suppress glioma cell proliferation and pro-inflammatory cell infiltration, and exhibit a good response to nimustine treatment
Dagıstan *et al*.[34]	2012	2.0 ATA, –	Rats with C6/LacZ glioma cell	Combination of HBOT with TMZ produced an important reduction in glioma growth and effective approach to the treatment of glioblastoma
Xie *et al*.[36]	2020	–, 60 min	Nude mice with paw-transplanted glioma	Vitexin could cooperate with HBOT to make the glioma radiotherapy sensitive
Zembrzuska *et al*.[37]	2019	2.0 ATA, 60 min	T98G glioblastoma cells	The combined usage of isothiourea derivatives and HBOT shows a promising therapeutic way for malignant glioma treatment
Yahara *et al*.[41]	2017	2.0 ATA, 60–90 min	24 patients with glioblastoma multiforme	The combined therapy of radiotherapy using intensity modulated radiotherapy after HBOT, combined with chemotherapy, was a possible and promising treatment modality for people with glioblastoma
Wang *et al*.[44]	2018	2.4 ATA, –	C57BL/6J mice, GL261-Luc cells	HBOT induced ROS signaling in the thymus, inhibited CD3+ T cell generation, and facilitated malignant glioma cell growth *in vivo* in the intracranial glioma mouse model
Ding *et al*.[45]	2015	3.0 ATA, 60 min	Rats with C6 glioma cells inoculation	HBOT alone may promote tumor growth, and is therefore not advisable to treat patients with gliomas and neurodeficits with HBO alone
Suzuki *et al*.[60]	2009	0.2 MPa, 60 min	6 patients with malignant or brainstem gliomas	HBOT prolongs the biological residence time of carboplatin
Kohshi *et al*.[61]	1996	–	21 patients with malignant glioma	HBOT combined with radiotherapy seems to be a useful form for malignant gliomas

ATA, atmospheres absolute; EGFP, enhanced green fluorescent protein; GBM, glioblastoma; HBOT, hyperbaric oxygen therapy; MPa, megapascal; ROS, reactive oxygen species; TMZ, temozolomide; –, not stated.

quently, it is essential to optimize HBOT strategies for future adjuvant therapy in glioblastoma.

Optimization of treatment protocols

Precision

Conduct in-depth research into the biological effect profiles, such as gene expression, signal pathway activation status, and functional changes, elicited by different HBOT parameters (including pressure, duration, frequency, and treatment course) across various glioblastoma models. Emphasis should be placed on molecular subtypes (e.g., IDH mutation, MGMT methylation status) to identify parameter sets that maximize anti-tumor efficacy while minimizing potential risks.

Individualization

Identify biomarkers predictive of HBOT efficacy and potential risk. As a primary effector molecule in the hypoxic response, HIF-1α serves as a robust indicator of tissue hypoxia severity. Concurrently, carbonic anhydrase IX (CA9/CAIX) has been widely implicated in tumor hypoxia and is associated with prognosis and treatment resistance across various cancer types. Furthermore, specific gene expression profiles, including markers of stemness such as CD133, CD15, and SOX2, could help select patients most likely to benefit from HBOT.

Timing

Precisely determine the optimal temporal combination of HBOT with radiotherapy and chemotherapy (e.g., before, during, or after radio/chemotherapy) and identify the optimal interval.

Exploration of novel combination therapy strategies

Given the potential impact of HBOT on the tumor microenvironment and immune function, its combination with emerging therapies holds considerable promise.

Immune checkpoint inhibitors

Ameliorating tumor hypoxia can reverse the immunosuppressive nature of the tumor microenvironment, leading to enhanced effector T-cell activity. Theoretically, HBOT has the potential to overcome hypoxia-mediated immune checkpoint inhibitor resistance. Clinical trials are needed to validate its safety and synergistic effects.

Targeted therapy

HBOT can activate pro-survival signaling pathways (e.g., VEGF, HIF, NF-κB); it is necessary to evaluate molecular inhibitors that target these pathways. Intricate crosstalk has been identified among the HIF, VEGF, and NF-κB signaling pathways, wherein ROS plays a critical role in mediating this interactive regulatory network. Therefore, investigating inhibitors directed against ROS is necessary. As noted previously, N-acetylcysteine emerges as a promising lead compound to initiate such investigative endeavors.

Tumor Treating Fields (TTFields)

Explore whether HBOT's effects on tumor cell proliferation and membrane potential influence TTFields efficacy.

Future research should address several key areas for advancement. First, we need to examine different molecular subtypes of glioblastoma. These are defined by IDH mutation status, MGMT promoter methylation, or stem cell markers CD133, CD15, and SOX2. It is important to evaluate HBOT parameters, such as treatment duration, frequency, and oxygen pressure. This will help find the best therapeutic plans for specific patient groups. Second, HBOT can activate pro-survival signaling pathways and stimulate neovascularization through ROS; combinatorial strategies that integrate HBOT with targeted agents warrant exploration.

Limitations

Several limitations of this review should be acknowledged. First, as a mini-review, it does not quantitatively synthesize data from all available studies, which may introduce selection bias during evidence interpretation. Second, the current clinical evidence base remains relatively immature: most studies are small-scale, non-randomized, and lack standardized protocols for HBOT administration. Future research should prioritize well-designed multicenter randomized controlled trials with standardized HBOT regimens, implement biomarker-driven patient stratification, and systematically explore combinatorial strategies with novel therapeutic approaches to validate the role of HBOT in the treatment of glioblastoma.

Conclusions

HBOT exhibits a dual role in glioblastoma treatment. On one hand, it has demonstrated potential anti-tumor benefits, including enhanced radiosensitivity and chemosensitivity, improvement of the tumor microenvironment, and attenuation of cancer stem cell properties. On the other hand, accumulating evidence suggests that HBOT may activate pro-survival signaling pathways, increase oxidative stress related genomic instability, and potentially facilitate tumor progression under certain conditions. Future research should focus on optimizing HBOT protocols, conducting rigorous clinical trials, and exploring synergistic combinations with established and emerging therapies, including radiochemotherapy, targeted agents, and immunotherapy, to safely and effectively integrate HBOT into comprehensive glioblastoma management.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Manuscript drafting (PW, NW), manuscript writing (SG), and manuscript revision (BL, LZ, JL). The publication has been approved by all co-authors.

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