Research Progress of Drug-loaded Hydrogels in the Treatment of Burn Infections

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Abstract Burn infection is one of the most common and severe complications in burn patients and a major factor contributing to high mortality rates. The loss of skin barrier function and the immunosuppressive state following burns make patients highly susceptible to wound infections, which can progress to systemic sepsis. Although burn wounds are initially sterile, they are rapidly colonized by Gram-positive bacteria (*e. g.*, *Staphylococcus aureus*) within a short period, followed by colonization with Gram-negative bacteria (*e. g.*, *Pseudomonas aeruginosa*), thereby increasing therapeutic challenges. Current clinical management relies on a multidisciplinary collaborative approach, combining conventional antibiotics, emerging therapies, and comprehensive care strategies. Among these methods, early intervention, precise treatment administration, and prevention and control are critical to improving patient survival and prognosis. In recent years, drug-loaded hydrogels, as a class of wound repair materials characterized by biocompatibility, controlled drug release, and multifunctional integration, have demonstrated significant advantages in the treatment of burn infections. They can effectively inhibit pathogenic microorganisms, alleviate inflammation, and promote tissue regeneration. This review systematically summarizes recent research advances in the application of drug-loaded hydrogels for the treatment of infected burn wounds, aiming to provide a reference for their further development and clinical translation.

Key words Burn infection; Wound dressing; Hydrogel; Wound healing promotion
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Burns are acute injuries to the skin and deeper tissues caused by external damaging factors such as thermal energy, chemicals, electricity, or ionizing radiation. They often result in severe local tissue destruction and can trigger intense systemic pathophysiological responses, affecting multiple systems including immunity, metabolism, and circulation. As a high-risk clinical condition, burns are associated with significant rates of disability and mortality[1]. During the progression of disease in burn patients, wound infection stands as one of the most common and serious complications. It not only significantly delays wound healing and induces a state of chronic inflammation, but is also closely associated with a decline in patient recovery quality and reduced survival rate[2-3]. Due to the presence of extensive necrotic tissue, accumulation of exudate, and local microenvironment disorder at burn wound sites, conditions become highly favorable for the colonization and proliferation of various pathogenic microorganisms such as bacteria and fungi. It significantly increases the risk of infection, which, in severe cases, can progress to sepsis and failure of multiple organs. Research has confirmed that burn-related infections are one of the important causes of sepsis[4].

Following the occurrence of a burn, the body's immune function becomes inhibited at multiple links, and the skin's natural barrier structure and function are disrupted. The wound is directly exposed to external pathogens, making it vulnerable to invasion by multidrug-resistant organisms (MDR), which significantly increases the difficulty of treatment[5]. Epidemiological data indicate that the incidence of wound infection in burn patients can reach 54.6%, with a continued upward trend as the prolongation of hospital stay increases. Infection not only intensifies local and systemic inflammatory responses, but may also promote the progression of partial-thickness burns to full-thickness skin necrosis, further worsening patients' condition[6]. Therefore, infection prevention and control in burn wounds has become a critical factor in improving prognosis.

The spectrum of pathogens causing burn wound infections is diverse, primarily including bacteria, fungi, and viruses. The infection process typically follows a staged evolution. It is initially dominated by Gram-positive bacteria (*e. g.*, *Staphylococcus aureus*)[7], which are subsequently replaced by Gram-negative bacteria (*e. g.*, *Pseudomonas aeruginosa*). Fungal infections (such as by *Aspergillus* and *Candida* species) are also on the rise, particularly in patients receiving long-term antibiotic therapy or whose wounds remain in a chronically moist environment[8]. Among these, *P. aeruginosa* has emerged as one of the most common multidrug-resistant organisms in burn infections due to its ability to form biofilms, significantly limiting the effectiveness of antimicrobial therapies[9]. In recent years, the rising prevalence of multidrug-resistant bacteria has further complicated the prevention, control, and treatment of burn infections[10]. Currently, the clinical management of infected burn wounds emphasizes a combined approach of early debridement and systemic antimicrobial therapy. Early surgical debridement can effectively remove necrotic tissue and colonizing pathogens, reducing the infectious burden and promoting wound healing[11]. However, the efficacy of traditional debridement methods is limited when managing specific types of

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injuries, such as chemical or explosion-related burns. Furthermore, although topical antimicrobial agents (*e. g.*, silver sulfadiazine cream) are widely used, their inhibitory effect against multidrug-resistant bacteria remains suboptimal[12]. Concurrently, the rational application of antibiotics is particularly critical. Excessive or inappropriate use not only accelerates the evolution of drug-resistant bacteria, but may also destroy the wound's microecological balance, paradoxically increasing the risk of infection[13]. Therefore, the treatment of burn infections requires a comprehensive multidisciplinary collaborative strategy, encompassing multiple aspects such as acute-phase management, wound repair, infection control, pain intervention, and long-term rehabilitation[14].

Given the limitations of conventional treatments in managing complex infected burn wounds, the exploration of novel, efficient and safe wound management strategies has become a research focus. In recent years, hydrogels have demonstrated significant promise in the fields of wound dressings and drug delivery, owing to their excellent biocompatibility, biodegradability, and controllable physicochemical properties[15-17]. Their high water content, softness, and responsiveness to external stimuli make them ideal drug carriers, enabling the stable loading and controlled release of antibiotics, anti-inflammatory factors, and growth factors[18]. The three-dimensional network structure of hydrogels not only allows for sustained drug release and reduction of systemic side effects, but also enables targeted delivery through the modulation of cross-linking density and composition, thereby optimizing therapeutic efficacy[19]. Furthermore, hydrogels can mimic the natural extracellular matrix, maintaining a moist wound environment to facilitate cell migration and proliferation. By incorporating antimicrobial or bioactive molecules, they enable precise intervention and accelerated healing of infected wounds. Although certain natural polymer-based hydrogels (*e. g.*, chitosan, cellulose, dextran) possess inherent antimicrobial properties[20], the design of most current drug-loaded hydrogels has incorporated synthetic antibiotics, metal ions, metal nanoparticles, and composite systems with natural polymers[21]. With advancements in material science and synthetic methods, novel intelligent delivery systems such as thermosensitive, light-controlled release, magnetically responsive, and multi-stimuli-responsive hydrogels are continuously emerging, offering more possibilities for anti-burn infection therapy[22].

Based on the aforementioned context, this review aims to systematically summarize recent research advances in drug-loaded hydrogels for combating burn infections. It focuses on analyzing the construction strategies, functional properties, current applications, and future prospects of different types of drug-loaded hydrogels in the treatment of infected burn wounds, with the goal of providing a reference for subsequent research and clinical translation.

Antibiotic-loaded Hydrogels

The destruction of the skin barrier and immune suppression caused by burns make patients highly susceptible to invasion by pathogens such as bacteria and fungi. Although conventional antibiotics remain the cornerstone of burn infection treatment, the increasing severity of drug resistance issues limits their long-term efficacy[23]. In contrast to systemic administration, antibiotic-loaded hydrogels enable localized targeted delivery, effectively reducing systemic toxicity and the risk of drug resistance, thereby demonstrating significant value in the treatment of infectious burns.

Methicillin-resistant *S. aureus* (MRSA) is one of the most common colonizing pathogens in burn wounds and is closely associated with high morbidity and mortality rates[23]. To address MRSA infection, Chhibber *et al.*[24] developed a local delivery system using a moxifloxacin-loaded chitosan-based hydrogel as an antibiofilm formulation. In a murine burn infection model, it significantly inhibited biofilm formation and reduced the severity of infection. Zhu *et al.*[25] constructed a heme-enriched Dex-HA hydrogel, which not only effectively inhibited MRSA and *Escherichia coli*, but also promoted epithelial re-epithelialization, enhanced extracellular matrix (ECM) remodeling, and significantly suppressed scar hyperplasia in a rat full-thickness burn infection model. Chen *et al.*[26] prepared a norfloxacin-loaded hydrogel using sodium carboxymethyl cellulose as the matrix for treating *P. aeruginosa*-induced burn wound sepsis and other skin infections. This formulation was non-irritating and overcame the limitations of oily ointments. Grolman *et al.*[27] evaluated the prophylactic therapeutic effect of a high-concentration minocycline/gentamicin agarose hydrogel in a porcine burn model. They determined that 0.5% agarose was the optimal concentration for viscosity and pH. The antibiotics remained stable in the gel and were released continuously for at least 7 d. Its efficacy in preventing infection and reducing burn depth was comparable to that of the clinically commonly used silver sulfadiazine cream, offering a novel approach for burn prophylaxis.

Hydrogels Loaded with Nanoscale Antimicrobial Materials

In recent years, the combination of metal nanoparticles with hydrogel matrices for creating intelligent dressings that possess both excellent antimicrobial properties and wound-healing capabilities has become a cutting-edge direction in burn care[28]. Among these, silver is widely recognized in wound management due to its broad-spectrum antimicrobial properties. Silver nanoparticles (AgNPs) can destory bacterial outer membranes, inhibit biofilm formation, and enhance antimicrobial effects through the synergistic interplay of size, morphology, and concentration[29-31]. Their mechanisms of action include binding to thiol groups in bacterial mitochondrial membrane proteins, reducing membrane potential, blocking the respiratory chain, and inhibiting ATP synthesis, thereby disrupting energy metabolism[29]. The study of Pangli *et al.*[31] demonstrated that incorporating AgNPs into chitosan hydrogels not only enhanced the structural properties, but also exhibited significant bactericidal activity against multiple pathogens, with the antimicrobial efficacy increasing in relation to the silver content. In the silver-doped chitosan hydrogel dressing developed by Xie *et al.*[32], AgNPs served as antimicrobial agents and improved the mechanical strength and structural integrity of the gel. This formulation showed superior bactericidal effects against *S. aureus* and *E. coli* compared with plain chitosan hydrogels.

Besides silver, other metal nanoparticles also hold potential. Copper ions can destroy bacterial structures by promoting the generation of reactive oxygen species (ROS). They are also taken up by bacteria, leading to energy depletion and DNA replication impairment, thereby exerting a multi-mechanistic synergistic antimicrobial effect[33-34]. Ren *et al.*[35] prepared a chitosan-based hydrogel (CS/GP) and loaded it with hydrothermally synthesized copper tin sulfide (Cu_3SnS_4) nanoparticles, constructing a CS/GP/Cu_3SnS_4 composite dressing. In a murine scald model, this material achieved sustained antibacterial activity through the gradual release of copper ions and significantly promoted wound repair. It demonstrated promising anti-infection and tissue regeneration capabilities, indicating potential for clinical application.

Hydrogels Loaded with Natural Antimicrobial Agents

In response to the increasingly severe issue of antibiotic resistance and the urgent demand for green biomaterials, hydrogels loaded with natural antimicrobial agents have emerged as a new direction in burn treatment due to their excellent biocompatibility, multi-target modes of action, and low toxicity.

Antimicrobial peptides (AMPs), short-chain cationic/amphipathic molecules of the innate immune system, offer advantages such as broad-spectrum antimicrobial activity, rapid bactericidal kinetics, and a low tendency to induce resistance[36]. In addition to their direct bactericidal effects, some AMPs can modulate inflammatory responses, promote cell migration and proliferation, and stimulate angiogenesis, thereby accelerating tissue repair[37-38]. However, their poor stability *in vivo* has made integrating them into wound dressings for local delivery and multifunctional therapy a key research focus. For example, one study constructed a macroporous hydrogel (DA7CG@C) loaded with the multifunctional antimicrobial peptide DP7 and placental mesenchymal stem cells (PMSCs). DP7 was immobilized on the surface of the cryogel via dopamine oxidative polymerization, enabling direct bactericidal activity and inflammation modulation during the inflammatory phase. During the proliferative phase, the internal PMSCs promoted the regeneration of skin, blood vessels, and hair follicles. In the remodeling phase, DP7 regulated the negative paracrine secretion of PMSCs, synergistically facilitating scarless wound healing[39]. Another study self-assembled the natural AMP Jelleine-1 into a hydrogel. The material significantly inhibited MRSA both *in vitro* and *in vivo* and promoted the healing of infected burn wounds[40].

Lipopeptides and other natural small molecules also hold potential. Colistin, an effective lipopeptide, was loaded into a self-healing hydrogel. Its storage modulus could be modulated by adjusting the degree of crosslinking and drug loading to meet the varying requirements of different wound healing stages. This hydrogel achieves the release of most of the drug within 24 h and maintains high efficacy against both sensitive and resistant *P. aeruginosa* in *in-vitro* antibacterial tests and animal infection models, suggesting its potential as a candidate for the local treatment of microbial infections in burn wounds[41].

Exosome-loaded hydrogels demonstrate advantages in promoting wound healing, yet traditional formulations still fall short in terms of shape adaptability and antimicrobial performance. One study addressed this by preparing a sprayable thermosensitive polysaccharide-based hydrogel (ADA-aPF127@LL18/Exo) via a Schiff base reaction, achieving sustained release of exosomes and enhanced antibacterial efficacy. In a deep partial-thickness burn model, this material significantly accelerated epithelialization, granulation tissue formation, and collagen deposition, induced hair follicle regeneration, and alleviated inflammation, finally promoting overall healing[42]. Another study involved grafting ε-polylysine (EPL) with epigallocatechin gallate (EGCG) to form EPL-EGCG. This was then combined with methacrylated gelatin (GelMA) and RGD sequences to construct a highly expansible interpenetrating network hydrogel. Further, multifunctional complexes (GelMA/EPL-EGCG/GM-PDA@PRP) were formed by integrating dopamine-coated GelMA microspheres and platelet-rich plasma (PRP). This material exhibited excellent hemostatic performance in liver and tail vein injury models. In an infected burn model, it demonstrated antimicrobial properties, promoted angiogenesis, and induced macrophage polarization toward an anti-inflammatory phenotype, offering a novel strategy for wound management prior to skin grafting[43]. Additionally, a hydrogel containing thymol showed significant inhibitory effects against *S. aureus*, *Klebsiella pneumoniae*, and other pathogens. In a rat burn model, a wound contraction rate of 55% was achieved within 15 d[44].

Multifunctional and Synergistic Therapeutic Hydrogels

Burn wound repair requires simultaneously addressing multiple challenges including infection control, inflammation regulation, and tissue regeneration. Multifunctional synergistic therapeutic hydrogels, which load multiple active components or integrate various functional modules to achieve integrated antibacterial, anti-inflammatory and pro-healing treatment, have become a central focus of current research.

Antibacterial-antiinflammatory synergy

The excessive inflammatory response triggered by persistent bacterial infection is a key pathological factor hindering wound healing and inducing scar hyperplasia and tissue necrosis. Xing *et al.*[45] developed an injectable alginate/chitosan hydrogel (PECE) loaded with quercetin. This system was constructed using oxidized sodium alginate (OAlg) via Schiff base and electrostatic interactions, with quercetin incorporated through hydrogen bonding for sustained release. PECE combined antibacterial and anti-inflammatory functions, effectively inhibiting *E. coli* and *S. aureus*, and it significantly downregulated the pro-inflammatory cytokines IL-6 and TNF-α secreted by macrophages. Animal experiments demonstrated that this hydrogel promoted angiogenesis and collagen deposition by reducing infection and inflammatory burden, thereby inhibiting scar formation.

Gong *et al.* [46] designed a liquid-absorbing antibacterial hydrogel (Cur-Mg@PP) loaded with a curcumin-magnesium polyphenol network. This hydrogel consisted of a base (PP) formed by ε-polylysine (ε-PLL) and γ-polyglutamic acid (γ-PGA), into which a curcumin-magnesium polyphenol network was introduced. Owing to the high water-absorbing capacity of ε-PLL and γ-PGA, the Cur-Mg@PP powder rapidly absorbed wound exudate and was transformed into a moist viscous gel, enabling the synergistic release of Mg^{2+} and curcumin (Cur). Together, these components exerted multiple effects including analgesia, antioxidant activity, anti-inflammatory action, angiogenesis promotion, and tissue regeneration, significantly accelerating burn wound healing.

Antibacterial-pro-healing synergy

Wound infection and delayed healing are central challenges in wound management, with over 6 million cases of chronic wounds worldwide annually attributed to bacterial infections. Antibacterial-pro-healing hydrogels combine biomimetic extracellular matrix properties with composite functionalities. They can achieve synergy between bactericidal action and tissue repair through the loading of antibacterial components or the construction of responsive systems.

One study used chemically modified hyaluronic acid (HA), dextran (Dex), and β-cyclodextrin (β-CD) as carriers to construct a composite hydrogel (Gel-Res/pDNA-VEGF) loaded with resveratrol (Res) and a plasmid encoding vascular endothelial growth factor (pDNA-VEGF). This system accelerated the healing of excisional burn wounds, demonstrating particularly significant effects in suppressing inflammation and promoting microvascular formation. It also exhibited good biocompatibility, indicating broad potential as a gene-delivery wound dressing[47].

Zhu *et al.* [25] prepared a sanguinarine (SA)-enriched SA/GMs/Dex-HA hydrogel (dextran-hyaluronic acid hydrogel incorporating gelatin microspheres). It exhibited high porosity and favorable swelling properties, promoting NIH-3T3 fibroblast proliferation and enabling sustained release of SA. *In-vitro* experiments confirmed its inhibitory effects against MRSA and *E. coli*. *In vivo*, in a rat full-thickness burn infection model, it exhibited dual antibacterial and pro-healing functions, improving re-epithelialization, promoting ECM remodeling, and suppressing scar formation through modulation of TGF-β1, TNF-α, and TGF-β3 expression.

Combined photothermal/photodynamic therapy (PTT/PDT)

Composite hydrogels integrating photothermal (PTT) and photodynamic (PDT) effects, often loaded with photothermal agents such as polydopamine or related nanoparticles, can generate heat under near-infrared (NIR) irradiation. This destorys bacterial biofilms, concentrates bactericidal action, and enhances antibiotic penetration, achieving physical-chemical synergistic antibacterial activity and precise drug release[48].

One study enhanced the solubility, antibacterial, and hemostatic properties of chitosan via quaternization modification. A thermosensitive polyphosphate crosslinker (PNDF) was then used to construct an antibacterial hydrogel, while polydopamine (PDA) was introduced to impart photothermal activity. This composite material enhanced antibacterial efficacy under near-infrared irradiation while also exhibiting hemostatic functions, effectively promoting burn wound repair in mice. Graphene oxide (GO), due to its good water dispersibility and NIR photothermal effect, enables its composite hydrogels to improve local blood supply, inhibit bacteria and inflammation, and facilitate chronic wound healing[49].

Another approach involved crosslinking the thermoresponsive copolymer poly(N-isopropylacrylamide) (PNIPAM, with its lower critical solution temperature (LCST) adjusted to body temperature) with dopamine-functionalized pectin hydrazide (PDAH) to prepare an injectable, biodegradable, and self-healing hydrogel. The hydrogel combined favorable mechanical properties, biocompatibility, and thermoresponsive sustained-release capabilities. Introducing GO imparted photothermal properties and enabled vancomycin loading. The system also exhibited pH-responsiveness, allowing for accelerated drug release under NIR irradiation. Ultmately, it promoted the repair of burn wounds by inhibiting bacterial growth[50].

Another study crosslinked carboxymethyl cellulose containing hydrazide groups and a hemostatic polyphosphate segment (CHP) with polydopamine-grafted oxidized pectin (OPD) to prepare a hemostatic self-healing hydrogel. The prepared polydopamine-coated graphene oxide (PGO) was loaded to impart photothermal antibacterial and reactive oxygen species (ROS)-scavenging capabilities, and tannic acid (TA) was further loaded to enhance antioxidant and anti-inflammatory properties. The PGO/TA/Gel composite hydrogel reduced infection and promoted cell proliferation both *in vitro* and *in vivo*. By mitigating inflammation and enhancing collagen deposition and angiogenesis, it significantly accelerated burn wound healing in mice[51].

Intelligent Responsive Drug-loaded hydrogels

Intelligent responsive drug-loaded hydrogels can sense signals from the pathological wound microenvironment (pH, ROS, enzymes, *etc.*), triggering precise drug release or functional activation to enable on-demand therapy. They significantly enhance therapeutic efficiency and specificity, representing a frontier direction in this field.

pH-responsive drug-loaded hydrogel

Infected wounds often exhibit an acidic pH (5.5–6.5) due to bacterial metabolism. This property can be leveraged using pH-sensitive structures such as Schiff base bonds or borate ester bonds to trigger the release of antimicrobial agents or growth factors. One study developed a pain-relief PGSB hydrogel dressing containing PVA crosslinked with GA, and incorporating SA, Zn^{2+}, and CS

@ BN nanoparticles. The physical and chemical crosslinking is realized by hydrogen bonds, ionic/coordination interactions, and dynamic borate ester bonds. The hydrogel combined high mechanical strength, self-healing properties, and injectability, integrating analgesic, antibacterial, anti-inflammatory, pro-angiogenic, and antioxidant functions. Its swelling and degradation exhibited pH-responsiveness (adapted for exudate absorption at pH 7.4 and wound healing progression at pH 5.8). It efficiently released Zn^{2+} and borax under acidic conditions, significantly accelerating the healing of infected burn wounds[52].

Another study constructed pH-sensitive vancomycin (VANCO)-loaded silk fibroin-alginate nanoparticles (NPs), embedded within a poly(N-isopropylacrylamide) (PNIPAM) hydrogel containing epidermal growth factor (EGF), for the treatment of chronic burn infections. The hydrogel allowed for modulation of the release rates of both the antibiotic and the growth factor. VANCO exhibited pH-responsive release behavior from the nanoparticles, with faster release under alkaline pH. *In vitro*, it promoted fibroblast proliferation. *In vivo*, when used to treat *S. aureus*-infected burn wounds in rats, it demonstrated superior outcomes compared with the control group in terms of epithelialization rate, wound contraction, and neovascularization. Additionally, TGF-β expression was enhanced, and infection was significantly reduced[53].

Huang *et al.*[54] constructed a QCS/OD/TOB/PPY@PDA self-healing hydrogel. Based on Schiff base cross-linking, it enabled pH-responsive release of tobramycin (TOB), and acidic environments could trigger on-demand release, preventing overuse. The hydrogel maintained bactericidal effects against *P. aeruginosa* and *S. aureus* for up to 11 d. *In vivo*, it effectively controlled inflammation, promoted collagen deposition and angiogenesis, and significantly accelerated the healing of infected burn wounds.

ROS-responsive drug-loaded hydrogel

Reactive oxygen species (ROS) levels are significantly elevated in wounds during the inflammatory phase and can serve as activation signals for functional responses. One study reported a hydrogel based on caffeic acid-functionalized short peptides, Nap-F3K-CA. It self-assembled via non-covalent interactions (with CA promoting assembly), allowing it to conform to irregular wounds and maintain a moist environment. It targeted high-ROS areas, possessed ROS-scavenging capabilities, and alleviated oxidative damage. Furtehrmore, it downregulated pro-inflammatory cytokines, exhibited potent antibacterial activity, and demonstrated good biocompatibility and hemostatic properties. *In-vivo* experiments demonstrated its ability to promote collagen deposition, vascular regeneration, and hair follicle formation, thereby accelerating the restoration of skin structure. It shows promising clinical potential[55].

Another study developed a self-healing hydroxyphenyl chitosan hydrogel (HPCS-EWH). It combined excellent biocompatibility with antioxidant, anti-inflammatory, and antimicrobial properties, inheriting the ROS-scavenging and antibacterial functions of its parent components. In a *S. aureus*-infected burn model, it accelerated healing, and promoted cell proliferation and angiogenesis. It is suitable for the treatment of deep partial-thickness burns[56].

Conclusions and Prospects

Although hydrogel-based drug delivery systems demonstrate significant potential in the treatment of infected burn wounds, their translation into clinical practice still faces several challenges. (1) Mechanical properties (strength, toughness) require further optimization to meet the mechanical demands of wounds with varying depths and morphologies. (2) Biocompatibility and the degradation rate must be precisely regulated to avoid material residue or premature degradation that could compromise efficacy. (3) Manufacturing processes are complex, with challenges remaining in optimizing drug loading efficiency, mechanical adaptability, and quality control for large-scale production. (4) Long-term safety and efficacy need thorough validation through comprehensive preclinical and clinical studies.

Looking to the future, leveraging advanced algorithms such as machine learning can accelerate the structural design and performance optimization of hydrogels, advancing the development of multifunctional integrated and intelligent responsive systems. Deepening interdisciplinary research in materials and biomaterials will enable the development of safer, more efficient, and personalized treatment strategies for infected burn wounds. It will ultimately improve patient outcomes and further broaden the clinical applications of hydrogel dressings.

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