REVIEW ARTICLE

REVISTA ENFERMAGEM ATUAL IN DERME

INTEGRATIVE REVIEW OF TOPICAL HEMOSTATIC AGENTS IN SURGERY

REVISIÓN INTEGRADORA DE AGENTES HEMOSTÁTICOS TÓPICOS EN CIRUGÍA

REVISÃO INTEGRATIVA DE AGENTES HEMOSTÁTICOS TÓPICOS EM CIRURGIA

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ABSTRACT
Background: Controlling bleeding during all operative periods is extremely important in order to achieve a good clinical outcome in interventional treatment, as significant blood loss can result in death. Therefore, it is important to better understand the hemostatic materials available. **Aim:** Describe, analyze, and categorize the evidence associated with the use of topical hemostatic agents in surgery. **Methods:** An integrative literature search was carried out through the PubMed database, in Portuguese, English and Spanish, using terms related to hemostatics for bleeding control. Abstracts were screened to determine relevance and, if necessary, appropriate additional review of the original articles. Based on these findings, this article provides a review of a variety of hemostatic agents (HA), from products clinically approved for human use, to recently developed concepts with great potential for use in in-hospital settings. These can be administered locally to control bleeding through different raw materials, presentations, and mechanisms of action. **Results:** Among the forty-two publications identified, eleven were selected because they met the inclusion criteria. **Conclusion:** Better knowledge of available topical hemostatics allows for a quick and effective blood management plan in order to achieve ideal results, such as reducing mortality and overall procedure time, contributing to faster recovery, and avoiding possible adverse events.
Keywords: Hemostatic materials; Polymer; Nanofibers; Medical use.

RESUMEN
Introducción: Controlar el sangrado durante todos los períodos operatorios es de suma importancia para lograr un buen resultado clínico en el tratamiento intervencionista, ya que una pérdida significativa de sangre puede provocar la muerte. Por tanto, es importante comprender mejor los materiales hemostáticos disponibles. **Objetivo:** Describir, analizar y categorizar la evidencia asociada al uso de agentes hemostáticos tópicos en cirugía. **Métodos:** Se realizó una búsqueda integradora de literatura a través de la base de datos PubMed, en portugués, inglés y español, utilizando términos relacionados con hemostáticos para el control de hemorragias. Se examinaron los resúmenes para determinar la relevancia y, de ser necesario, una revisión adicional apropiada de los artículos originales. Con base en estos hallazgos, este artículo proporciona una revisión de una variedad de agentes hemostáticos (HA), desde productos clínicamente aprobados para uso humano, hasta conceptos desarrollados recientemente con gran potencial para su uso en entornos hospitalarios. Estos HA pueden administrarse localmente para controlar el sangrado a través de diferentes materias primas, presentaciones y mecanismos de acción. **Resultados:** De las cuarenta y dos publicaciones identificadas, se seleccionaron once porque cumplían con los criterios de inclusión. **Conclusión:** Un mejor conocimiento de los hemostáticos tópicos disponibles permite un plan de manejo sanguíneo rápido y efectivo para lograr resultados ideales, como reducir la mortalidad y el tiempo general del procedimiento, contribuir a una recuperación más rápida y evitar posibles eventos adversos.
Palabras clave: Materiales hemostáticos; Polímero; Nanofibras; Uso médico.

RESUMO
Introdução: O controle do sangramento em todos os períodos operatórios é de suma importância, a fim de se alcançar bom desfecho clínico no tratamento intervencionista, já que a perda de sangue significativa pode resultar em morte. Portanto, é importante compreender melhor os materiais hemostáticos disponíveis. **Objetivo:** Descrever, analisar e categorizar as evidências associadas ao uso de agentes hemostáticos tópicos em cirurgia. **Métodos:** Foi realizada uma pesquisa integrativa da literatura através da base de dados PubMed, nos idiomas português, inglês e espanhol, utilizando termos relacionados a hemostáticos para controle de sangramento. Os resumos foram selecionados para determinar a relevância e, se era necessária, uma revisão adicional adequada dos artigos originais. Com base nessas descobertas, este artigo fornece uma revisão de uma variedade de agentes hemostáticos (AH), desde produtos clinicamente aprovados para uso humano, até conceitos recentemente desenvolvidos, com grande potencial para uso em ambientes intra-hospitalares. Estes AH podem ser administrados localmente para controle do sangramento através de diferentes matérias-primas, apresentações e mecanismos de ação. **Resultados:** Dentre as quarenta e duas publicações identificadas, onze foram selecionadas por atenderem aos critérios de inclusão. **Conclusão:** O melhor conhecimento dos hemostáticos tópicos disponíveis permite um plano de manejo sanguíneo rápido e eficaz, a fim de alcançar resultados ideais, como redução da mortalidade e do tempo geral do procedimento, contribuindo para uma recuperação mais rápida e evitando possíveis eventos adversos.
Palavras-chave: Materiais hemostáticos; Polímero; Nanofibras; Uso médico.

INTRODUCTION

Bleeding caused by trauma or surgery is a serious health problem and uncontrollable bleeding can result in death. It is therefore important to develop safe, effective, and convenient hemostatic materials. The active hemostatic agents (HA) currently used to investigate the field of hemostasis are divided into four broad categories: natural polymers, synthetic polymers, inorganic materials, and metal-containing materials. Hemostatic materials are prepared in various forms for wound treatment applications based on the active ingredients used. These materials include nanofibers, gels, sponges, and nanoparticles. HAs find their applications in the field of wound care and are also used for hemostasis during surgery, especially for malignant tumors, since fast and effective hemostasis can reduce the possibility of tumor cells spreading with blood, as well as reducing the volume lost[1].

The amount of blood in a healthy person remains relatively constant throughout their life, and blood volume is proportional to body weight[2]. When blood loss reaches 20% of total blood volume, it becomes difficult to maintain normal blood volume and arterial blood pressure. When the extent of blood loss exceeds 40% in a short time, potentially fatal conditions develop if the blood is not transfused in time[3].

Bleeding in the cranial cavity presents unique challenges in the field of neurosurgery. Neurosurgeons at the end of the 19th century used ill-adapted general surgical instruments, which were crude tools from the pre-antiseptic era[4].

Scientific and technological advances demand specific knowledge and constant learning from health professionals in order to offer the highest quality of service[5]. Eventually, instruments were developed to help with intra- and post-operative hemostasis. Understanding this history is important for future improvements and innovations in a field with considerable specificities. The different methods for achieving hemostasis are grouped into three categories: mechanical, chemical, and thermal[1].

It is therefore important to control the extent of bleeding. Bleeding control in tissue injuries is achieved through a series of physiological events, such as vasoconstriction, platelet thrombosis, and blood coagulation[6]. Considering the importance of evidence-based practice (EBP), this study seeks to answer the following question: does the new generation of hemostatic materials in surgery maintain patient safety and, consequently, avoid possible risks and complications?

Therefore, this study aimed to describe, analyze, and categorize the evidence associated with the use of topical HA in surgery, in order to help control bleeding at all surgical times.

METHODS

A literature review was carried out using the PubMed Central database (National Library of Medicine – National Center for Biotechnology Information). All articles related to the use of topical HA published in the last five years (2019-2024), open access, available in full, in Portuguese, English, and Spanish, were analyzed. The keywords used to obtain these articles were: hemostatic materials, polymers, nanofibers, and medical use.

The search in the databases was restricted to PubMed, as there are more publications in this specific field. However, terms such as "Neurosurgery"; "Hemostatics"; "Hemostasis"; and "Pediatrics" were disregarded because they limited the search, indicating a possible low, or even non-existent, number of publications on the subject. Adding "Surgery" to the keywords resulted in the same search results. However, by replacing "Surgery" with "Neurosurgery", no articles were found.

The abstracts were screened to determine their relevance and, if necessary, an appropriate additional review of the original articles was conducted, as they did not fully meet the inclusion criteria.

Based on these findings, this article provides a review of a variety of new HAs, from clinically-approved for human use products to recently developed concepts with great potential for use in in-hospital settings. These HAs can be administered locally to control bleeding through different raw materials, presentations, and mechanisms of action.

The theoretical framework adopted was EBP, which emphasizes the use of research to guide clinical decision-making and requires learning specific skills for the different processes used to evaluate articles analytically and reflectively. Therefore, EBP combines research and the clinical competence of the professional who provides the service and the preferences of patients to make a decision about a specific problem[7].

Evidence is defined as the presence of facts or signs that clearly show that something exists and is true, in other words, evidence is proof or demonstration that something might be legally submitted to the determination of the truth of a topic[8,9].

An adapted six-stage classification was proposed to evaluate the evidence from the studies: 1st Stage: identifying the topic and selecting the guiding research question; 2nd Stage: establishing criteria for including and excluding the studies; 3rd Stage: defining the information to be extracted from the selected studies and categorizing them; 4th Stage: evaluating the studies included in the review; 5th Stage: interpreting the results; 6th Stage: presenting the review and synthesizing the knowledge[10]. This classification considers the methodological approach of the study, the design used in the research, and its rigor. Thus, the systematic analysis of the articles involved: title, year, objectives, design, main results, and recommendations.

RESULTS

This review presents different HAs, with variations in their raw materials, presentations for use, and information on their efficacy in helping hemostasis and the healing process in surgical wounds. We also present the results obtained when various HAs based on nanomaterials were

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studied. Finally, we focus on the pros and cons of the various forms of HAs and report on the application prospects and importance of these biotechnologies in the health field. The data presented here provide a perspective for future research directions, which will continue to focus on the importance of hemostasis and healing. It is believed that there will be an increase in adjuvant topical HA options, with biotechnology continuing to play a key role within this context.

Forty-two articles were found, but only eleven of them met the objective of this study. A summary of the articles included in this integrative review is presented (Table 1).

Table 1 - Articles associated with the use of topical hemostatic agents in surgery

Material	Form	Test model	Effectiveness	Ref.
Natural polymers, synthetic polymers, inorganic and metal-containing materials	Chitosan-based nanofibers (CS) Gelatin and collagen sponges (COL) Natural polysaccharides Hydrogels	Review of multiple controlled studies	Nanofibers based on chitosan, gelatin and collagen sponges, hydrogels and other natural polysaccharides can cause allergic reactions. Hemostatic materials prepared in the form of hydrogels and sponges adhere well to injured tissues. Synthetic polymers have low bioactivity. Inorganic materials demonstrate long-term physical and chemical stability without biotoxicity. Metal ions give hemostatic materials better efficacy and antimicrobial properties.	[1]
Electrospun amino acids	Nanofibers prepared by electrospinning different polymers	Review of multiple controlled studies	Nanofibers are widely researched and applied due to their size on the nanoscale. Currently, single polymer electrospinning can no longer meet the requirements for hemostatic agents.	[11]
Nanocellulose, obtained by fermentation of the bacterium Komagataeibacter xylinus with TEMPO oxidation (OBNC) Angiogenic drug deferoxamine (DFO)	OBNC sponge OBNC-DFO sponge	Randomized clinical trials, *in vitro* (in a rat tail amputation model) and *in vivo* (in a liver trauma model)	DFO was associated via an amide bond and promoted clot formation, activating a coagulation reaction by rapid blood absorption due to the high all-pore area. The additional release of DFO stimulated the secretion of HIF-1α and the reconstruction of blood flow, thus achieving rapid hemostasis and vascularization in damaged tissues. High water absorption capacity, at a rate of approximately 1.70g/s, rapidly increased clot formation in the initial phase of hemostasis. Coagulation in *in vitro* and *in vivo* experiments with OBNC and OBNC-DFO showed procoagulation effects superior to those of collagen hemostatic sponges (COL). OBNC and OBNC-DFO sponges promoted aggregation and activation of red blood cells and platelets with shorter whole blood coagulation time, more robust activation of coagulation pathways, and less blood loss. In the *in vitro* cellular assays, OBNC-	[12]

			DFO prevailed over OBNC in promoting the proliferation of human umbilical vein endothelial cells (HUVECs). In addition, the release of DFO improved the secretion of HIF-1α, further strengthening the damaged vascularization, indicating the achievement of structural and functional regeneration of the injured area. This is a new and highly promising HA, as it is a biomaterial and has pro-vascular regeneration effects, rapidly activating coagulation pathways and enabling skin regeneration.	
Hemostatic aerogel made of time-oxidized nanofibers	Nanocellulose-collagen-chitosan nanofibers (TCNF-COL-CS)	Randomized clinical trials, *in vitro* (evaluation of antibacterial, cytotoxic, hemostatic degradation properties)	*In vitro* coagulation experiments revealed the favorable procoagulant properties of TCNF/COL/CS along with high adhesion to erythrocytes and platelets. TCNF/COL/CS aerogel significantly increased hemostatic efficacy by 59.8% and decreased blood loss by 62.2% in the liver injury model when compared to Surgicel® (the most widely used HA). In addition, it showed excellent biodegradability both *in vitro* and *in vivo*, and a substantial increase in resistance (96.8% against E. coli and 95.4% against S. aureus) compared to TCNF. The significant hemostatic and biodegradable characteristics of TCNF/COL/CS can be attributed to its interconnected porous structure, greater porosity, and efficient water absorption, together with the synergistic effect of its three constituents. The new plant-derived nanocellulose composite aerogel has excellent antibacterial and hemostatic characteristics, as well as greater biocompatibility *in vivo*.	[13]
Nitric oxide (NO) donor S-nitrosoglutathione (GSNO) mixed with polyhydroxybutyrate (PHB) and a polylactic acid (PLA)	NO-releasing antimicrobial nanofibers adapted for blood contact applications	Quasi-experimental studies, such as non-randomized clinical trial, single group before and after test, time series or case control	The NO-releasing nanofibers successfully reduced the count of viable adhered bacteria by ~80% after 24 hours of exposure to Staphylococcus aureus. When exposed to porcine plasma, they reduced platelet adhesion by 64.6% compared to control nanofibers. They were also found to be non-cytotoxic (>95% viability) to NIH/3T3 mouse fibroblasts, and staining with DAPI and phalloidin showed that fibroblasts cultured on NO-releasing fibers improved cell adhesion and functionality. Therefore, these new NO-releasing nanofibers provide safe antimicrobial and hemocompatible coating for medical devices that come into contact with blood.	[14]
Bioabsorbable protein-	Nanofibers	*In vitro* and *in*	When the nanofibers with thrombin are	[15]

polymer and thrombin electrospun fiber system	prepared with PEO – poly(ethylene oxide), loaded by non-covalent coupling of thrombin	*vivo* tests	in contact with the injured tissue, the presence of water in the skin or blood catalyzes the degradation of the membranes, thus releasing thrombin. Thrombin then accelerates the coagulation process, promoting rapid hemostasis. In contrast to other hemostatic materials, PEO/thrombin nanofibers do not require mechanical removal after application, and the viscoelastic nature of such biomaterials allows them to conform to a variety of wound topographies. Notably, PEO/thrombin are promising functional materials, and their use is a powerful strategy for hemostatic treatment, from simple first aid and wound sealing to minor surgical procedures. Biocompatible and easy to use.	
Nanofibers with additional hydrophobic poly(dimethylsiloxane) coating	Chitosan (CS)/poly(ethylene oxide) (PEO) nanofibers with poly(dimethylsiloxane)	Quasi-experimental studies, such as non-randomized clinical trials, single group before and after tests, time series, or case-control	Chitosan (CS)/poly(ethylene oxide) (PEO) nanofibers alone are capable of initiating the healing and regeneration process at a very early stage of injury. The unmodified nanofibers showed a highly porous structure with the presence of uniform, randomly aligned nanofibers, in contrast to coated materials in which almost all the free spaces were filled with poly(dimethylsiloxane). Coating with hydrophobic poly(dimethylsiloxane) (applied to favor the removal of nanofibers from the wound surface) impacted porosity and decreased mechanical properties and adherence to excised human skin, although the values obtained were comparable to those obtained for commercial materials similar to hydrofibers, composed of sodium carboxymethylcellulose or calcium alginate. *In vitro* cytotoxicity and irritation studies showed biocompatibility and no irritant response of the nanofibers in contact with a three-dimensional model of reconstituted human skin, while the scratch test using the HDFa human fibroblast cell line revealed the valuable potential of CS/PEO nanofibers to promote cell migration at an early stage of injury.	[16]
Mineralized hybrid hydrogels	Polyvinyl alcohol (PVA) mineralized sodium alginate (Alg) hydrogels and TEMPO-oxidized cellulose nanofibers	*In vitro* tests with HFB-4 and HSF skin cells to preliminarily investigate cytotoxicity and cell viability in the presence of the proposed	The presence of HFB-4 and HSF skin cells confirmed a low cytotoxicity of the mineralized hybrid hydrogels and also highlighted a significant increase in cell viability. These preliminary results suggest promising use of mineralized hybrid hydrogels based on Alg/PVA/TCNFs for bone and wound healing applications.	[17]

	(TCNFs)	materials		
Electrospun biopolymers that are resistant to bacteria and repair tissues	PVA-chitosan-collagen-licorice nanofibrils (PCCLNM)	*In vitro*	A disk diffusion method was used to investigate antibacterial properties, revealing strong activity against the bacterium Staphylococcus aureus (S. aureus), with an inhibition zone of 20 mm, due to the chemical constituents of the licorice and chitosan compound. As PVA was used to provide structural strength, licorice and chitosan intrinsically have antibacterial properties, while collagen nanofiber helps cell growth as it is an important protein for connective tissues. The results of this study show the bacterial resistance, moderate moisture management properties, and intrinsic biocompatibility of the bio-based nanofibrous hemostat. It can be concluded that PCCLNM is a promising candidate for use as a material for healing injured tissues.	[18]
Hemostatics with different types of bioelastomers	Porous 3D nanofiber sponge with synthesized and electrospun polyurethane (PU) cross-linked with glutaraldehyde (GA) and Gel (gelatin) – PU-TA/Gel	*In vitro*, liver injury in rats	The PU-TA/Gel sponge had the highest porosity and water absorption rate and exhibited cytocompatibility, negligible hemolysis, and shorter clotting time. It also rapidly induced stable blood clots with shorter hemostasis time and lower bleeding volume in a rat liver injury model. These results showed that PU-TA/Gel-based sponges can offer an alternative platform for hemostasis and wound healing.	[19]
Hydrogels with antibacterial double quaternized chitosan (DQC) with cystamine-based non-isocyanate polyurethane (NIPU-Cys) and cellulose nanofibrils (TEMPO-CNF)	Biocompatible, 3D printable antimicrobial hydrogels composed of DQC, NIPU-Cys and TEMPO-CNF	*In vitro*	The resulting hydrogels were found to be suitable materials for 3D printing using a direct ink writing (DIW) technique, producing porous, biocompatible hydrogels endowed with valuable attributes suitable for various biomedical applications, such as hemostasis and wound healing. The incorporation of DQC had minor effects on the printability of the ink and the mechanical properties of the hydrogel structures, presumably due to the disruption of the ordered network. In addition, the hydrogel inks exhibited favorable thinning behavior along with efficient and rapid gelation, making them suitable for 3D DIW printing. In addition, the hydrogel inks exhibited favorable thinning behavior, along with efficient and rapid gelation, making them suitable for 3D DIW printing. The hydrogels also exhibited good swelling rates and porous architecture, making them particularly suitable for	[20]

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			applications such as treating injured tissue. Importantly, the introduction of DQC increased *in vitro* cell proliferation in the structures without negatively impacting viability. This indicates that the slightly cytotoxic tendencies of quaternary chitosan diminish when it is present in a NIPU-CNF matrix. Therefore, the combination of DQC in a NIPU-Cys- CNF matrix appears as a promising composition for the elaboration of porous, biocompatible, and 3D printable hydrogels with excellent swelling properties. These materials have significant potential as constituents for creating biocompatible materials for various biomedical applications.	

DISCUSSION

Data from this study was very useful for starting discussions on the use of new biotechnologies such as topical HA in surgery. Three aspects are considered the main ones regarding hemostatic agents (HA): whether they have active hemostatic ingredients, the form of the materials and their applications in medical specificities. There are four main categories of materials used to achieve hemostasis: natural polymers, synthetic polymers, inorganic materials, and metal-containing materials.

Chitosan-based nanofibers, hemostatic sponges, and hydrogels have been used to obtain satisfactory results in animal models characterized by low bleeding volumes. However, the same performance could not be achieved in wounds with excessive bleeding.

Synthetic polymers are readily available and can be produced in bulk and modified in convenient and functional ways. However, their low bioactivity impairs their practical application.

Inorganic materials have demonstrated long-term physical and chemical stability without biotoxicity. But, for example, zeolite emits a lot of heat when it encounters water or blood. This results in an increase in the local temperature of the surgical wound, which can cause skin burns and hinder the patient’s healing and recovery process. The various metal ions used to prepare hemostatic materials give the materials excellent antibacterial properties, as well as improve the coagulation efficiency of hemostatic materials.

There is a growing trend to design intelligent hemostatic materials that can mimic natural hemostatic processes. For example, platelet mimics that promote thrombus formation and fibrin-structured nanofibers that facilitate clot formation could point to the development of new hemostatic materials. Currently, the most commercially available HAs are designed for large, flat wounds, and materials must be developed to treat deep, irregular wounds. Flexible hemostatic materials that adhere firmly to the surrounding tissue should be developed, even

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when bleeding is excessive, making them difficult to adhere to.

Due to their nanoscale size, nanofibers can mimic the structure of the human extracellular membrane effectively, as well as their porosity, high specific surface area, and other characteristics with good air permeability and moisture retention. Electrospinning, an important method for preparing nanofibers, has also been a major research theme in recent years.

Nowadays, new electrospinning techniques are combined with a variety of polymers with compatible or complementary properties, selected to be mixed with inorganic nanoparticles, drugs, and bioactive substances in order to obtain nanofibers with parallel, coaxial and triaxial structures, which can be used to aid hemostasis, topical antimicrobial action and accelerated wound healing, as well as in the areas of transportation and controlled release of drugs, as well as reducing complications, such as encapsulation of active substances, among others.

The electrospinning of various compatible or complementary polymers associated with inorganic nanoparticles, medicines, and bioactive substances has also been applied in the areas of hemostasis, antimicrobial action, and accelerated healing of injured tissues.

CONCLUSIONS

The recent development of hemostatic biomaterials is relevant to biomedical applications, as they are needed as adjuvants in the process of preventing and controlling bleeding. As such, they are an important step in wound healing and the prevention of serious and diverse health problems.

Given the history of artificial hemostasis using mechanical, physical, or chemical methods, current research has included biocompatible products based on nanofibers, with antimicrobial action or not, prepared by electrospinning various polymers, for example, based on chitosan, gelatin, collagen, oxidized nanocellulose, natural polysaccharides, and hydrogels. Better knowledge of these newly available topical hemostatics allows for a quick and effective blood management plan in order to achieve optimal results, such as reducing mortality and overall procedure time, contributing to a faster recovery, and avoiding possible adverse events, such as post-operative complications caused by allergies, cytotoxicity and encapsulation of synthetic materials, as well as the need for blood transfusions and increased costs.

Future studies should prioritize patient safety and modularize the creation of mechanisms similar to the physiological process of coagulation, allowing the improvement of various materials and technologies in order to find the ideal system to promote and strengthen the active aggregation of platelets and consequent local formation of the fibrin network, accelerating the healing process.

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Authorship criteria (authors' contributions)

• **Rafael Colodetti =** 1. contributed substantially to the design and/or planning of the study; 2. in obtaining, analyzing and/or interpreting the data; 3. as well as in the writing and/or critical review and final approval of the published version;

• **João Augusto Diniz Moura =** 2. in obtaining, analyzing and/or interpreting the data; 3. as well as in the writing and/or critical review and final approval of the published version;

• **Lorena Souza Rittberg Maurício =** 2. in obtaining, analyzing and/or interpreting the data;

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• **Débora Kiyo Kissimot Gusmão =** 2. in obtaining, analyzing and/or interpreting the data; 3. as well as in the writing and/or critical review and final approval of the published version;

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• **Sonia Alves Gouvea =** 1. contributed substantially to the design and/or planning of the study; 2. in obtaining, analyzing and/or interpreting the data; 3. as well as in the writing and/or critical review and final approval of the published version.

Declaration of conflict of interest

Nothing to declare

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