Review

Reduction in the late infection rate of cranioplasty: a retrospective review in porous hydroxyapatite prosthesis

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SUMMARY: ***Aims.*** *The present paper aims to give an overview of the occurrence of infections in cranioplasty procedures with different custom-made metallic, polymeric and ceramic implants. Post-operative infections are the most serious complication amongst the graft versus host response. To date, only few studies have tried to investigate the biomaterial/host interaction in in vivo conditions, but none highlighting the real influence of the material used (either a polymer or a metal) on the extent of bacterial proliferation.*
Materials and methods. *With incoming evidence from a narrative review to support their use in literature revision, a Medline search was conducted on PubMed for published articles reporting on complications related to cranioplasty materials, with particular focus to cranioplasty infections. Papers concerning pre-clinical studies (where available), surgical procedures, intra-operative cranioplasty complications and pediatrics were excluded; timing for cranioplasty and prognostic factors were excluded; case series that merely mention materials of choice for cranioplasty were excluded; technical notes, letters, and editorials were excluded; not-downloadable texts were excluded; papers concerning only autologous bone complications / infections were excluded. Duplicate records were screened. Thorough bibliographic searches of qualifying articles was performed to identify additional articles for inclusion.*
Results. *The analysis highlights enhanced bacterial resistance in porous hydroxyapatite scaffolds, in comparison with other metallic or polymeric implant, particularly in the long term.*
Conclusions. *Considering the excellent osteogenic and osteointegrative ability of porous hydroxyapatite scaffolds, as demonstrated by several previous works, this finding supports the use of biomimetic calcium posphate scaffolds for more effective and safer applications in bone regeneration, particularly in large cranial reconstruction.*

KEY WORDS: *Cranioplasty, Infection, Porous hydroxyapatite.*

INTRODUCTION

Nowadays, intensive research is dedicated to the development of novel biomaterials and medical devices to be used as grafts in reconstructive surgery (e.g. to repair cardiovascular, musculoskeletal, dental tissues), with the purpose to enhance their therapeutic effectiveness, safety and *durability*.

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LIST OF ACRONYMS AND ABBREVIATIONS: **3D** = three-Dimensional; AB = **CBS** = CustomBone Service; **Ca/P** = Calcium/Phosphate; **CT** = Computed Tomography; **Ti-CP** = Titanium Commercially Pure; **DC** = Decompressive Craniectomy; **HA** = HydroxyApatite; **MRI** = Magnetic Resonance Imaging; **PEEK** = PolyEtherEtheKetone; **PHA** = Porous HydroxyApatite; **PMMA** = PolyMethylMethAcrylate; **RCT** = Randomized Controlled Trial; vs = versus.

Particular attention is given to prevent post-surgical drawbacks and to possibly extend the use of medical devices along prolonged time, thus limiting the recourse to painful and costly revision surgery. In this respect, *graft versus host response* represents one of the most important and serious concerns in clinical practice, particularly when manifesting in post-operative complications such as infections[1,48,65]. Infections can be classified as "early" and "late". Early infections, occurring in the first follow-up period (1-3 months), are usually consequence of the patients' debilitated clinical conditions, which predispose to an increased risk of complications[36,71], or can occur through intra-operative contaminations in the operating room, even though the control of sterility has progressed during years. These events are mainly independent on the material used. By the other side, late post-op infections (> 3 months follow-up) are instead often caused by haematogenous infections starting at the implant site, where bacteria colonize the implant, proliferate and spread on the body, forming a biofilm resistant to the host's immune system or to antibiotics[11,20,60]. Independently on their onset, such events are highly undesirable. However, while "early" infections can be managed in the immediate post-operative period with debridement and local antibiotic therapies to attempt prosthesis retention, in majority of the cases "late" post-op infections require revision surgery with scaffold removal, followed by intensive antibiotic therapies and additional surgical treatments[28,72].

Intensive discussion is emerging on whether the intrinsic chemico-physical features of a medical device can affect its interaction with bacteria[10].

In this regard, some of these aspects have been investigated in past studies, trying to find a clear rationale that determines which physicochemical characteristics are relevant for the adhesion and proliferation of infective bacteria[35,53]. However, most of the existing studies describing the bacteria-biomaterials interaction have been carried out *in vitro* and animal models[5,18,34]. This can hardly predict the typical behavior of a synthetic biomaterial in real clinical practice, where the environment is governed by long-term self-regulating, buffering mechanisms and is characterized by complex biochemical and enzymatic reactions not easily reproducible by *in vitro* and *in vivo* models. By the other side, even though various studies report that ceramics may prevent or limit bacterial infections in comparison with metals[51,52], none of them have shown a clear relationship between the material used and the extent of bacterial proliferation[21,55]. As such, with the lack of exhaustive or comparative studies shedding light on the key factors responsible for biofilm formation, it is difficult to obtain clear protocols for designing biomaterials with inherent anti-bacterial characteristics. In this respect, the analysis of clinical cases reporting on post-operative infections of implanted devices can be the initial source for shedding light on the most relevant mechanisms for the occurrence of bacterial infections in vivo. An application field in medicine where biomaterials of different nature are used and can be compared to analyse the occurrence of infections is cranioplasty, a neurosurgical procedure aimed at restoring large cranial defects. In this respect, it is highly desired that cranioplasty implants elicit good and long-lasting mechanical and aesthetic result and, also, that such implants can live thoroughly along the patient's life with no need of removal[2]. Therefore, the possibility to limit the occurrence of infections in cranioplasty, or even to contrast them without need of the prosthesis removal[29] is a major clinical need.

A variety of biomaterials, from autologous bone to PMMA, PEEK, titanium, and calcium-based ceramics are used in cranioplasty. However, none of the materials currently available for cranial reconstruction is free from drawbacks. This includes autologous bone, still considered the "gold standard" material in spite of the high incidence of infection and bone resorption (29% to more than 50% in adults to 80% in paediatrics[7,22,25,30], Martin et al.[47] polymeric or metallic materials (i.e. titanium, PMMA or PEEK), which have reported relevant incidence of infections, enhanced cold/heat conduction and osteopenia induced by mismatch in stiffness at the bone/implant interface[7,22,14,67].

As alternative to the above-mentioned materials, HA, a ceramic material widely used in cranioplasty, is reported as elective for bone reconstruction, supported by countless studies reporting its excellent biocompatibility, osteoconductivity and osteointegrative properties when developed as porous scaffolds[16,37,38].

These features are related to its composition closely mimicking the mineral phase of human bone that favour cell adhesion, proliferation and osteogenic differentiation. Unlike PEEK, PMMA, titanium or Ti-CP alloys, HA can establish a chemical/biochemical continuity with host bone tissue, inducing the formation of a protective film made of "slime muco-polysaccharide deposits" at the surface, which may provide resistance to bacterial proliferation[12]. Recent studies report that calcium phosphates including HA demonstrate inherent antibacterial properties and good eukaryotic *vs* prokaryotic cell selectivity[3,58,69]. Due to its inherent nano/microporosity inducing higher specific surface area, HA has also good potential for *in situ* application of antibiotics. Thanks to these features, HA shows benefits in terms of enhanced regenerative and antibacterial properties.

With this in mind, the present paper aims to provide a comprehensive picture of the *short- and long-term performance* of different biomaterials, including HA, designed for cranial reconstruction, by exploring the occurrence of post-op infections. In particular, clinical data related to a porous HA implant have been compared with exhaustive literature data related to the use of titanium implants and other materials in cranioplasty[28,40]. The results are comparatively discussed, with the purpose of highlighting possible mechanisms relating to the physico-chemical and morphological characteristics of the implants with the healing process in the short- and long-term period.

□ METHODS

With incoming evidence from a narrative review to support their use in literature revision, a search was conducted on PubMed in the period between 2015 and 2024 for reviews, systematic reviews and meta-analyses on cranioplasty complications, including infections. The search was performed by filtering for 'cranioplasty infections', 'complications cranioplasty material' and 'complications cranioplasty infection'. The present analysis will focus only on customized implants specifically designed on the patient's 3D CT scan data, therefore omitting hand-made cranioplasty devices (i.e. cements), which are usually manufactured in the operating room. Papers concerning intra-operative cranioplasty, surgical procedures and paediatrics were excluded, as well as timing for cranioplasty and prognostic factors cranioplasty. Case series that merely mention material choice were excluded. Technical notes, letters, and editorials were excluded. Not-downloadable texts were excluded. Duplicate records were screened. All the reviews and meta-analyses selected were screened to identify additional articles and clinical studies for inclusion.

□ RESULTS

The search identified 114 papers spanning between 2015 and 2024. Of these, the following were excluded because of duplicates (n = 26), related to surgery procedures (n = 46), related only to the cranioplasty materials (n = 2), paediatrics (n = 10), storage procedures (n = 7), timing cranioplasty (n = 9), letter to editor (n = 2). Four papers were excluded because of flaws in the synthesis and analysis. Three papers related to the management of neurosurgical infections were considered for discussion, but not reported clinical data. At the end, five systematic reviews/meta-analyses reporting on clinical data about complications cranioplasties, including infection, were revised carefully[24,41,42,46,50,63,64].

Four of them[24,27,32,41,46,54,64], compared autologous bone with various synthetic materials (usually, PEEK, PMMA, titanium and HA), whereas only one[50] compared complications cranioplasty only deriving from heterologous solutions.

All the Authors reported high heterogeneity of clinical data. Malcolm et al.[46] included only one randomised clinical trial (autograft *vs* titanium) and 11 cohort studies (either retrospective or prospective). Liu et al. (2020)[42] identified three randomized studies[4,23] (autologous bone *vs* titanium and PMMA, autologous bone *vs* titanium and HA *vs* titanium, respectively), the remainder were observational retrospective or prospective studies, the majority of which single centre and only one multicentre study. van de Vijfeijken et al.[64] included two randomized studies[40] (autologous bone *vs* titanium and HA *vs* titanium, respectively), the all remnant were case series, case reports, cohort studies or were of retrospective design. Henry et al.[24] identified two randomized studies[26,40] (autologous bone *vs* titanium and HA *vs* titanium, respectively), the remainder were all but one retrospective cohort studies. Finally, Morselli et al.[50] identified only one randomized study[28] (HA *vs* titanium), the remainder were either retrospective or prospective studies.

Among all, at the end, there was only one randomized, prospective clinical study comparing two synthetic cranioplasty materials, i.e. HA *vs* titanium.

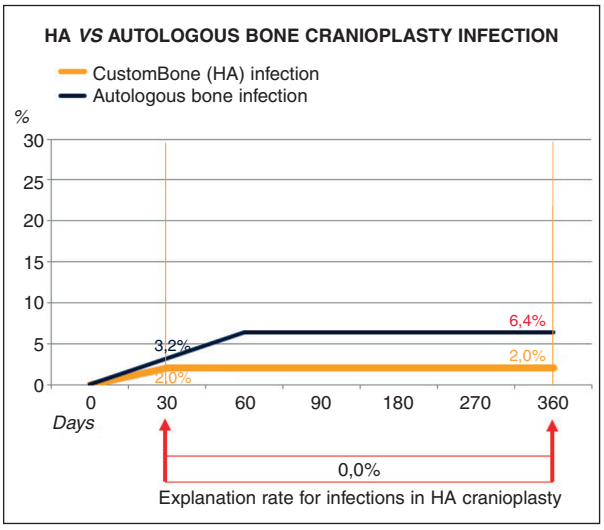

Figure 1. Post-operative infection evolution in a comparative cranioplasty study (HA *vs* autologous bone) (*original unpublished graph*).

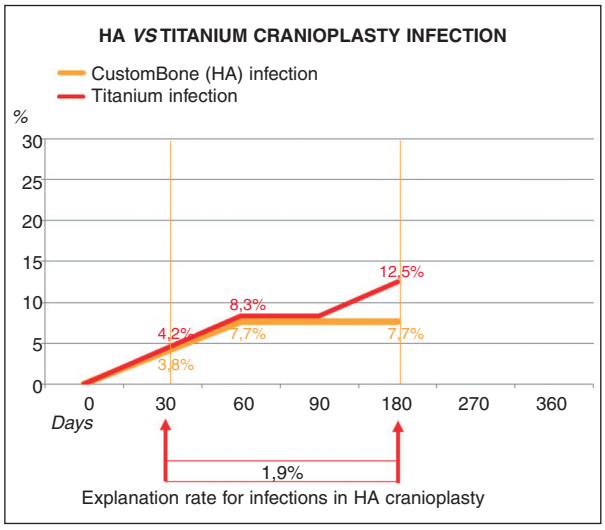

Figure 2. Post-operative infection evolution in a randomized, comparative cranioplasty study (HA *vs* titanium) (*original unpublished graph*).

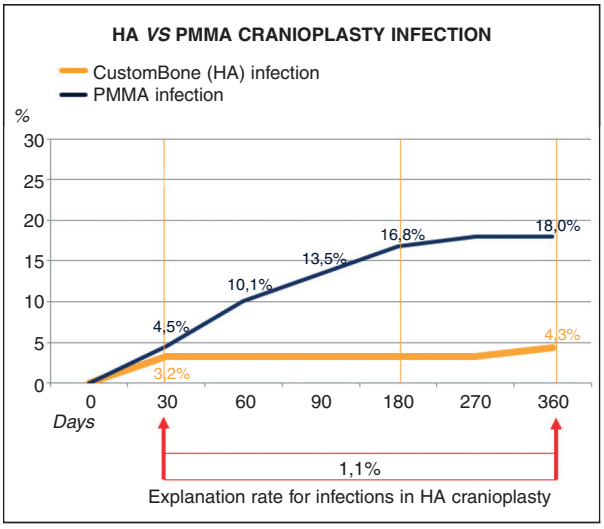

Figure 3. Post-operative infection evolution in a retrospective, comparative cranioplasty study (HA *vs* PMMA) (*original unpublished graph*).

The few remaining RCT included in the reviews compared autologous bone with synthetic materials. HA, titanium, PEEK and PMMA showed superior performances and safety profiles as compared to autograft. Liu et al. (2006)[41] and Malcolm et al.[46] reported lower complications with synthetic materials as compared to autograft (pooled data). van de Vijfeijken[64] reported 3.3% infections for HA, 5.4% for titanium, 5.9% for PEEK, 6.9% for autograft and 7.8% for PMMA, and the lowest removal rate for HA (overall: 2.5%), the greatest for autograft (overall 10.4%). Henry et al.[24] reported a pooled infection rate of infection of 6% with HA, as compared to PMMA (12%), titanium (8%) and autologous bone (8%). Morselli et al.[50] reported lower infection rates with the use of HA (7.3%), as compared to PMMA (10.5%), PEEK (7.3%) and titanium (10.5%). Explanation following infection was lower with the use of HA (5.9%), as compared to PMMA (10.2%), PEEK (6%) and titanium (7.7%).

Among the synthetic solutions, all the reviews reported a lower propensity for infection with HA. In order to further investigate the behaviour of HA in relation to infections, all the clinical studies included in the systematic reviews were screened to identify additional information on the composition and chemico-physical features of the HA employed in the studies, which resulted to be all but one performed with a HA-porous customized implant available on the market named, CustomBone Service CBS (Finceramica SpA, Faenza, Italy).

Clinical data available for the device CBS were further identified and deeply investigated. Among all the publications available to date for CBS, three prospective multicentre studies[19,28,40] compared infections between HA and synthetic materials, which results we decided to display with comparative graphs (*Figure 1, 2 and 3*), and *Table 1*.

In a prospective, comparative, multicentre, clinical

Author (*year*)	Type of study	Follow-up	Material	Pts (N.)	N. of surgical revisions for infection (%)			
					Total	T0/T30	T30/T180	T180/T360
Iaccarino et al. (*2015*)[28]	prospective, multicenter	12 months	**CustomBone** Autologous bone	**50** 31	**1 (2,0%)** 2 (6,4%)	**1 (2,0%)** 1 (3,2%)	ND ND	**0 (0,0%)** 1 (3,2%)
Lindner et al. (*2017*)[40]	prospective, randomized, multicenter	6 months	**CustomBone** Titanium	**26** 24	**2 (7,7%)** 3 (12,5%)	**1 (3,8%)** 1 (4,1%)	**1 (3,8%)** 2 (8,3%)	NA NA
Ganau et al. (*2020*)[19]	prospective, single-center	12 months	**CustomBone** PMMA	**92** 89	**4 (4,3%)** 16 (17,9%)	**3 (3,2%)** 4 (4,5%)	**0 (0,0%)** 12 (13,4%)	**1 (1,0%)** 4 (4,5%)

Table 1. Clinical Data HA ceramic implant *vs* other solutions (Multicentric and Single-Center Clinical Study). *Legenda:* N. = number; Pts = Patients; T0 = Time after implant placement; T30 = 30 days after implant; T180 = 30 days after implant; T360 = 360 days after implant.

study, Iaccarino et al.[40] showed lower post-operative infection rate (2%) of CBS as compared to autologous bone (6.4%) at one-year follow-up. As clearly outlined in *Figure 1*, the rate of infection for CBS turned stable after the first month from implantation, whereas the rate of infection for titanium cranioplasties increase over time.

In a randomised, comparative, multicentre clinical trial (the only to date comparing two synthetic materials for cranioplasty), Lindner et al.[40] showed lower infection rate (7.7%) of HA CBS as compared to titanium (12.5%) at 6 months follow-up. After two months from implantation, the rate of infection in the HA group was stable, while titanium implants showed a constant increase over time (*Figure 2*).

In a retrospective, comparative, long-term multicentre clinical trial, Ganau et al.[19] showed a lower infection rate (4.3%) of HA as compared to PMMA (18%) at one-year follow-up. The incidence of infection in the HA group was stable during the follow-up period, whereas in the PMMA group the infection rate increased over time up to 18% (*Figure 3*).

□ DISCUSSION

The analysis of clinical data here reported put in evidence that a certain rate of infections occurs within the first 60 days from implantation, irrespective of the investigated material. However, in the long-term period, infections in cranioplasties like autologous bone, titanium or PMMA tend to increase constantly, as compared to HA-based solutions. As such, it is reasonable to suppose that the inherent physicochemical features of the HA implant can play a relevant role for such a different performance. In this respect, which might be the factors making hydroxyapatite more resistant to bacterial infections, as compared to metals or polymers? When a scaffold is introduced into the human body, its chemical composition, surface texture and roughness, pore size and distribution and also mechanical properties - such as the stiffness - altogether play an important role in modulating the *foreign body reaction*, which represents the host's inflammatory response to an exogenous material. This interaction usually occurs and resolves within the first two to four weeks following the device implantation, even though the foreign body reaction at the tissue/material interface is present for the *in vivo* lifetime of the medical device. In this preliminary time lapse, it is expected that bone cells adhere to the implant, forming new bone tissue and establishing a tight interface with the implant, which is a key aspect for the scaffold stability and the subsequent stages of extensive colonization by the new bone. The host's inflammatory response to an exogenous material (divided in acute and chronic response) usually resolves quickly and is confined to the implant site. With biocompatible materials, early resolution of the acute and chronic inflammatory responses lasts no longer than two weeks. The persistence of the acute and/or inflammatory responses beyond 3 weeks usually indicates an adverse reaction against the foreign body, which can manifest in the development of an infection. These infections have been reported to occur in as many as 5 to 10% of patients with implanted prosthetic devices and represents the major source of morbidity and mortality[33].

In light of these considerations, it can be devised that

the physicochemical features of the implant play a pivotal role in determining the occurrence of infections, particularly in the late stage.

HA-based prostheses like CustomBone Service are made of porous, highly crystalline HA, a biocompatible and osteoconductive Ca/P material, with a chemical composition (range Ca/P = 1.65-1.82) and structure that resembles the mineral component (average Ca/P = 1.71) of human bones. This biomaterial is highly porous (range of porosity 35-65%), with a trabecular structure and multi-scale pore size are essential to ensure new bone penetration in the inner part of the scaffold and adequate exchange of nutrients and physiological liquids to provide new bone formation.

The association of a composition close to the mineral bone and the presence of wide-open and interconnected porosity are features making porous HA as very effective for extensive osteoconduction and osteointegration. This has a great relevance for bone regeneration, particularly in cranioplasty procedures, to give stability to the bone-implant interface that facilitates new bone apposition and proliferation in large bone defects thus permitting the faster recovery of the original biomechanical performance.

PEEK, PMMA, Titanium or Ti-CP alloys are all biocompatible materials widely used in bone surgery, but none of them has a chemical composition very similar to the natural bone as hydroxyapatite. Thanks to molecular recognition exerted by cells, HA substrates permit direct cells adhesion, as compared to other materials which usually interact with cells either via: i) a layer of apatite covering the implant surface due to supersaturation of surrounding physiological fluids, rich in Ca and PO4 ions, as occurring with titanium or silica-based materials[39,61]; or ii) through a fibrous tissue layer. Such latter case is particularly undesired, as fibrous tissues do not possess the same physicochemical, mechanical and biological properties of mature bone and may generate mechanical mismatches and related micro-movements, detrimental to callus formation, vascularization and possibly leading to inflammation and ultimately infections[9,44,59,68]. The activation of biomimetic recognition mechanisms by cells allows foreign bodies to be accepted by our physiologic system with increased safety; this is confirmed by the high number of titanium or polymeric devices successfully implanted so far. However, impaired reactions at the cell level can occur in a significant number of cases, more easily if the scaffold features are poorly affine with the host tissues, so that revision surgery after 10-20 years is a very frequent issue. Particularly, in case of polymeric implants a general concern is related to the production of free radicals as well as acidic and harmful by-products due to non-enzymatic dissolution, which may alter cell metabolism and vitality, and jeopardize tissue healing, particularly in the case of large bone defects[41]. Impaired cell activity due to such phenomena is a possible reason for the existence of persistent inflammatory states and consequent possible alteration of the immune system, potentially leading to proliferation of infective bacterial strains[4].

With the above considerations, it appears that bone-like composition and structure able to favour the natural physiological homeostasis and metabolic processes, can be relevant factors that not only promote extensive bone regeneration, but at the same time are able to establish unfavourable conditions for adhesion and proliferation of bacteria and infective strains. Conversely, in the presence of materials with limited affinity with cells, the clinical outcome can be affected by impairing foreign body reaction that are greatly depending on many different factors, also including gender or age-related conditions, with possible adverse reactions and infections also in the long term. In the undesired event of infections in neurosurgery, scaffold removal, is the only possible solution to avoid further complications, particularly if the meninges and underlying neural tissues are at risk. The recourse of revision surgery significantly increases the patient morbidity and raise healthcare costs but, more importantly, can raise the risks of secondary infections[13]. In this respect, the use of porous materials with ability to adsorb and retain drugs in their structure may offer significant advances, thanks to the possibility to perform antibiotic therapies directly in situ, possibly avoiding the removal of the original implant. HA implants can be fabricated by a variety of processing techniques with possibility to tailor multi-scale porosity, specific surface area, surface roughness and the hydrophilic character[56,57]. These properties are functional to uptake significant amount of antibiotic drug that can be released over a prolonged time lapse and with controlled kinetics[43,62]. This is relevant for more effective drug delivery profile that help to provide a sustained antibiotic therapy and to bypass the drawbacks and ineffectiveness related to systemic administration[31]. With the above considerations, macro porous, osteointegrative HA implants confirm as safe, versatile and effective devices for large bone reconstruction, particularly

suitable for cranioplasty procedures. Such a conclusion is supported by previous clinical studies, post-marketing surveillance activities and specifically focused case reports[6,8,28,40,45,49, 59,60,66,70]. In addition, the present outline of clinical cases confirms the capability of HA implants to prevent bacterial infections. Inherent antibacterial properties in biomaterials such as hydroxyapatite open to the possibility to reduce, or make more effective, the use of antibiotic drugs in bone surgery, thus aiding to contrast the ever increasing bacterial resistance to antibiotics, which is today a primary cause of increased adverse outcomes and increasing cause of death in the post-operatory period[17]. In a wider perspective, this may also have invaluable positive impact when considering the increasing number of patients in developing countries, for which the clinical and economic impact of pathogen resistance to drugs is expected to provide a huge burden to the community in the incoming years[15].

□ CONCLUSIONS

The outline of clinical cases shown in the present work provides a focus on the occurrence of post-op infections in cranioplasty procedures and highlights enhanced bacterial resistance in porous HA scaffolds, in comparison with other metallic or polymeric implant, in the long term. CaP scaffolds have been claimed as elective bone biomaterials since decades. The overview here presented confirms the advanced bio-functionality of hydroxyapatite and suggests that the use of bone scaffolds with close compositional and structural mimicry with the host tissue is a preferable approach to improve the clinical outcome, safety and the socio economic impact, with particular reference to cranioplasty procedures.

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