New Anti-Infective Coatings of Medical Implants

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Implantable devices are highly susceptible to infection and are therefore a major risk in surgery. The present work presents a novel strategy to prevent the formation of a biofilm on polytetrafluoroethylene (PTFE) grafts. PTFE grafts were coated with gentamicin and teicoplanin incorporated into different lipid-like carriers under aseptic conditions in a dipping process. Poly-β,1-lactic acid, tocopherol acetate, the diglyceride Softisan 649, and the triglyceride Dynasan 118 were used as drug carriers. The drug release kinetics, anti-infective characteristics, biocompatibility, and hemocompatibility of the coatings developed were studied. All coatings showed an initial drug burst, followed by a low continuous drug release over 96 h. The dimension of release kinetics depended on the carrier used. All coated prostheses reduced bacterial growth drastically over 24 h, even below pathologically relevant concentrations. Different cytotoxic levels could be observed, revealing tocopherol acetate as the most promising biocompatible carrier. A possible reason for the highly cytotoxic effect of Softisan 649 could be assessed by demonstrating incorporated lipids in the cell soma with Oil Red O staining. Tromboelastography studies, enzyme-linked immunosorbent assays, and an amidolytic substrate assay could confirm the hemocompatibility of individual coatings. The development of the biodegradable drug delivery systems described here and in vitro studies of those systems highlight the most important requirements for effective as well as compatible anti-infective coatings of PTFE grafts. Through continuous local release, high drug levels can be produced at only the targeted area and physiological bacterial proliferation can be completely inhibited, while biocompatibility as well as hemocompatibility can be ensured.

A major risk associated with surgical placement of medical implants such as endoprostheses or vascular prostheses is their high infection rate (4, 8). This is not only of prime importance for the patient but also imposes a high financial cost on the economy (21). Synthetic vascular grafts such as polytetrafluoroethylene (PTFE) prostheses are easily accessible to pathogens, mostly Staphylococcus aureus and Staphylococcus epidermidis. These pathogens colonize the implant by adhering to the patient’s own proteins located on the surface of the graft and form a biofilm (1, 14, 16, 23, 34). The formation of biofilms on biomaterials presents challenging complications in the field of medical implants (2, 12, 24, 28, 30). In a biofilm, bacteria are well protected from the host immune defense. An increase in antibiotic resistance is the consequence (6, 8, 35); even high local concentrations of antibiotics do not completely eradicate bacteria in biofilms (8, 10). It is therefore of great importance to prevent bacterial adhesion on vascular grafts (7). This can be achieved by antibiotic surface coatings.

There have been several approaches to equipping vascular grafts with anti-infective agents to prevent bacterial colonization. Different antimicrobial agents have been used (3, 5), as well as different ways to bind those drugs onto the surface of a PTFE prosthesis. A common method used to bind hydrophilic drugs onto the lipophilic surfaces of PTFE grafts is the use of surfactant-mediated agents, e.g., benzalkonium chloride (15, 18) or tri-dodecylmethylammonium chloride (17). Another method of drug binding is the incorporation of drugs into biodegradable polymer carriers (13).

The present work presents new lipid-based formulations to incorporate antibiotics for anti-infective action in grafts. Through local release, high drug levels can be attained at the targeted area only, and pathogenic colonization of the graft can be prevented.

PTFE grafts were coated with lipophilic agents such as poly-β,1-lactic acid (PDLLA), tocopherol acetate, the diglyceride Softisan 649, and the triglyceride Dynasan 118 as carriers for gentamicin and teicoplanin. An overall in vitro study assessing the release kinetics as well as the cytotoxicities, anti-infective characteristics, and hemocompatibilities of the corresponding coatings was performed.

MATERIALS AND METHODS

Medical implants. Commercially available PTFE grafts with a diameter of 6 mm (Alpha Graft PTFE; Alpha Research Deutschland GmbH, Berlin, Germany) were studied. Sterile grafts were cut into 1-cm lengths under aseptic conditions in a laminar airflow. The average weight of four 1-cm-long samples was assessed by weighing each sample three times, because weight standards are more accurate than length measurements.

Anti-infective coating. (i) Drug carriers. A defined mass of each of the following drug carriers was weighed out in a glass vial.

(a) PDLLA. Resomer R203H, purchased from Boehringer Ingelheim (Ingelheim, Germany), is a polymer of PDLLA with a molecular size of 29,000 Da. It is a racemic mixture of β and ε-enantiomers of lactic acid and is well studied as a biodegradable coating for medical implants.

(b) Softisan 649. Softisan 649 (Sasol Germany GmbH, Witten, Germany) is a partial ester of diglycerin containing medium-chain fatty acids, isostearic acid, stearic acid, 12-hydroxystearic acid, and adipic acid. It can be sterilized by heat and has a stable viscosity from 25 to 75°C similar to that of lanolin. It is referred to below as DG, for diglyceride.

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Coating process. Four different drug carriers were used for incorporating gentamicin sulfate as well as teicoplanin at a concentration of 10%. The implants were coated with the carrier containing the drug by two dip-coating procedures, ensuring a regular polymer coating, and are referred to below as drug-carrier-coated PTFE prostheses. The dip-coating procedure was carried out in sterile glass vials in the presence of a magnetic stir bar on a magnetic stirrer (RET basic IKAMAG; IKA) for 5 min, with a drying period of 5 min between the two coating procedures. All coating steps were carried out under aseptic conditions in a laminar airflow hood. For cytotoxicity tests, some grafts were coated in the same way with the drug carriers alone, without drugs; these control grafts are referred to below as drug-carrier-coated PTFE prostheses. The weight of each coating, as well as the amount of drug incorporated, was assessed by the difference in weight before and after the coating procedure. Because the surface of a PTFE prosthesis is not plane and regular and shows many pores, the thickness of individual coatings could not be reliably determined. In order to control the reproducibility of the quantity of coating and the drug dose per sample, and in order to minimize mistakes caused by inexact lengths of 1-cm samples of PTFE prostheses, the weights of PTFE prostheses before and after the coating procedures were assessed, and a coating quotient \( (Q) \) was established.

Morphological analysis-SEM. Drug release from drug-carrier-coated PTFE prostheses \((n = 3); \text{length, } 1 \text{ cm}; \text{diameter, } 6 \text{ mm}\) was studied in phosphate-buffered saline (PBS) at 37°C (pH 7.4) and 300 rpm in a Thermomixer (Fa. Eppendorf, Hamburg, Germany). Rotation was preferred to static state in order to simulate blood flow conditions in the vascular system. Uncoated PTFE prostheses served as the control. At 15 min and 1, 4, 8, 24, 48, 72, and 96 h, the elution medium was completely changed. Sample drug solutions were assayed for gentamicin by spectrophotometry. For this purpose, gentamicin was treated with a 1.25% aqueous ninhydrin solution at 95°C for 15 min, and absorption was measured at 405 nm. Teicoplanin concentrations were determined by an Innofluor teicoplanin assay system (Opus Diagnostics, Fort Lee, NJ).

Test bacterium. For in vitro studies, a clinical isolate of \(S. aureus\) (ATCC 49230) was used. The test strain was susceptible to both gentamicin (MIC, 0.5 mg/liter) and teicoplanin (MIC, 0.25 mg/liter). \(S. aureus\) was cultivated on Columbia agar plates (Becton Dickinson GmbH, Heidelberg, Germany) at 37°C for 18 h before testing.

Growth curve. In order to correlate the optical density (OD) at 600 nm (GeneQuant pro; Biochrom, Cambridge, United Kingdom) of an \(S. aureus\) suspension with the CFU of the microorganism, a growth curve was recorded at different time points in Mueller-Hinton broth (catalog no. 277570; BD Diagnostic Systems, Dieren, Heidelberg, Germany) at 37°C with a double-wavelength enzyme immunoassay for plasma prothrombin activation fragment (F1+2) values (Enzygnost F1+2 micro; Behring, Marburg, Germany). BTDA-blood plasma was tested for C3a-desArg (Complement C3a-desArg ELISA, Progen Biotechnik GmbH, Heidelberg, Germany). Thromboglobulin for whole blood was tested with a roTEG coagulation analyzer using the in-TEM reagent (both from Pentapharm GmbH, Munich, Germany) for analyzing the intrinsic pathway of blood coagulation.
RESULTS

Morphological analysis. Stable and regular coatings could be observed by SEM after dip-coating. All coated grafts retained their flexibility and had open pores for penetration on both sides (Fig. 1a to d).

Antibiotic release. The weights of 1-cm-long PTFE prostheses averaged 76.80 mg and varied more than 10%, leading to the conclusion that measuring 1-cm lengths of PTFE prostheses is less accurate than weighing. Coatings consisting of PDLLA with incorporated gentamicin showed an average $Q_c$ of 0.52, corresponding to a coating weight of 39.94 mg for the average 1-cm-long PTFE prosthesis, whereas the $Q_c$s of coatings consisting of PDDLA with incorporated teicoplanin averaged 0.32, corresponding to a coating weight of 24.58 mg. Tocopherol acetate-based coatings showed $Q_c$s of 0.25 (coating weight, 19.2 mg) for incorporated gentamicin and 0.23 (coating weight, 17.67 mg) for teicoplanin. The $Q_c$s of coatings with DG averaged 0.24 (coating weight, 18.43 mg) for incorporated gentamicin and 0.25 (coating weight, 19.2 mg) for incorporated teicoplanin. Coatings consisting of TG with gentamicin showed a $Q_c$ of 0.29 (coating weight, 22.72 mg), and TG coatings with teicoplanin had a $Q_c$ of 0.31 (coating weight, 23.81 mg) (Fig. 2).

Reliable reproducibility was demonstrated for the coating procedure with TA, DG, and TG. The average $Q_c$ of PDLLA with incorporated gentamicin is statistically different from the average $Q_c$ of PDLLA with incorporated teicoplanin.

To obtain information about time-dependent drug kinetics,
the release rates (defined as the total amount of drug released, in micrograms per hour) of gentamicin or teicoplanin present in the respective carriers were plotted against time. Continuous drug release kinetics could be demonstrated over 96 h for the four individual carriers (PDLLA, TA, DG, and TG). In the first hour an initial drug burst was observed, followed by a low continuous release of gentamicin for the rest of the testing interval. The carriers TA and DG showed comparable release the four individual carriers (PDLLA, TA, DG, and TG). In the ous drug release kinetics could be demonstrated over 96 h for the release rates (defined as the total amount of drug released, defined as the total amount of drug released, in micrograms per hour) of gentamicin or teicoplanin present in the respective carriers were plotted against time. Continuous drug release kinetics could be demonstrated over 96 h for the four individual carriers (PDLLA, TA, DG, and TG). In the first hour an initial drug burst was observed, followed by a low continuous release of gentamicin for the rest of the testing interval. The carriers TA and DG showed comparable release rates for incorporated gentamicin after 15 min: 2,403.1 μg/h and 2,121.6 μg/h, respectively. For gentamicin in PDLLA, a much higher release rate after 15 min, 4,528 μg/h, could be assessed, whereas the lowest release rate, 1,167.0 μg/h, was detected for gentamicin in TG. After 96 h, release rates for all four individual carriers ranged from 0.5 μg/h for PDLLA to 0.1 μg/h for TG.

For teicoplanin, an initial drug burst in the first hour was detected, followed by continuous drug release for the rest of the testing time. The release rates of the four individual carriers after 15 min ranged from 6,090.0 μg/h for PDLLA to 1,477.7 μg/h for TA, decreasing almost exponentially.

Continuous drug release over 96 h fulfills the primary aim of developing an effective anti-infective method for postoperative protection against infection. The total amount of the drug is expected to be released as the lipid-based carrier degrades over 1 to 6 months, which implies extended protection for this period.

Gentamicin and teicoplanin each showed a distinct pattern of drug release with the four different lipid-based carriers. Gentamicin and teicoplanin were stable in PBS in experiments for at least 96 h.

**Antibacterial characteristics.** Continuous antibiotic release for more than 1 day after a surgical procedure is one important aspect of the coatings, but the key characteristic is the antibacterial effect. Individual coatings showed a highly effective potency against pathologically relevant S. aureus concentrations in the range of 10^2 to 10^4 CFU/ml. There was no difference between ODs from samples and sterile Mueller-Hinton medium. Colony growth on agar plates incubated with sample media could not be observed with any of the individual coatings, leading to the conclusion that the individual coatings caused total germ eradication.

Bacterial growth in highly concentrated bacterial suspensions of 2 × 10^6 CFU/ml could be reduced by all drug-carrier-coated PTFE prostheses developed. For all coatings using gentamicin, a pathogen reduction rate of >99% after 24 h was observed. After 5 h of incubation, a decrease in CFU counts relative to those on uncoated prostheses was observed. While the number of S. aureus colonies in reference tubes increases during subsequent incubation, drug-carrier-coated samples show no additional growth. The best growth inhibition effect after 24 h was observed for the combination of PDLLA and gentamicin, resulting in a colony reduction rate of 99.42% (Table 1).

Coatings with teicoplanin showed a reduction in the S. aureus concentration after 24 h of at least 93.14% (with TA as the drug carrier) and as high as 99.43% (with PDLLA) (Table 1). The first growth inhibition effects can also be detected after 5 h of incubation.

**Adhesion of viable bacteria and antimicrobial potency after 24 h of elution.** Bacterial adhesion on 1-cm coated grafts after 24 h of incubation in an S. aureus suspension was determined. All gentamicin and teicoplanin coatings showed visibly reduced numbers of adherent pathogens on surfaces. The lowest numbers of pathogens on gentamicin coatings were observed on the surfaces of DG-based coatings, with average counts of 67 CFU, whereas PDLLA-based coatings showed the highest counts, at an average of 5,433 CFU. Reference pathogen numbers could not be assessed because they were far beyond visual determination, building up a bacterial mat even after two 1:10 dilution steps were carried out (Table 2). Inhibition zones on S. aureus lawns could not be detected for any of the four gentamicin coatings. For tested coatings with incorporated teicoplanin, the lowest number of adsorbed bacteria was found on the surfaces of PDLLA-based coatings, at an average of 120 counts, whereas TA-based coatings averaged 14,956 counts. Inhibition zones could not be detected for any of the four teicoplanin coatings.

**In vitro cytotoxicity studies.** The WST-1 assay shows high metabolic activity of viable L929 fibroblasts from mouse connective tissue in the presence of PTFE prostheses coated with

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**TABLE 1. Reductions in S. aureus concentrations in drug-carrier-coated PTFE prostheses from those in uncoated PTFE prostheses after 24 h of incubation in an S. aureus suspension**

<table>
<thead>
<tr>
<th>Type of coating</th>
<th>Colony reduction (%)</th>
</tr>
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<tbody>
<tr>
<td>G1</td>
<td>99.42</td>
</tr>
<tr>
<td>G2</td>
<td>99.35</td>
</tr>
<tr>
<td>G3</td>
<td>99.36</td>
</tr>
<tr>
<td>G4</td>
<td>99.31</td>
</tr>
<tr>
<td>T1</td>
<td>99.43</td>
</tr>
<tr>
<td>T2</td>
<td>93.14</td>
</tr>
<tr>
<td>T3</td>
<td>99.48</td>
</tr>
<tr>
<td>T4</td>
<td>94.53</td>
</tr>
<tr>
<td>Uncoated PTFE prosthesis</td>
<td>0</td>
</tr>
</tbody>
</table>

*a The initial S. aureus concentration was 2 × 10^6 CFU/ml. After 24 h in the presence of an uncoated PTFE prosthesis, the S. aureus concentration was 5,381.06 × 10^6 CFU/ml.

*b G1, 10% gentamicin in PDLLA; G2, 10% gentamicin in tocopherol acetate; G3, 10% gentamicin in Softisan 649; G4, 10% gentamicin in Dynasan 118; T1, 10% teicoplanin in PDLLA; T2, 10% teicoplanin in tocopherol acetate; T3, 10% teicoplanin in Softisan 649; T4, 10% teicoplanin in Dynasan 118.*

**TABLE 2. Averaged numbers of S. aureus colonies adsorbed on the surfaces of drug-carrier-coated PTFE prostheses after 24 h of incubation in a 2 × 10^6-CFU/ml suspension**

<table>
<thead>
<tr>
<th>Coating type</th>
<th>Averaged counts of adherent CFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>5,433 ± 9.411</td>
</tr>
<tr>
<td>G2</td>
<td>1,967 ± 3.748</td>
</tr>
<tr>
<td>G3</td>
<td>67 ± 58</td>
</tr>
<tr>
<td>G4</td>
<td>600 ± 1,039</td>
</tr>
<tr>
<td>T1</td>
<td>123 ± 70</td>
</tr>
<tr>
<td>T2</td>
<td>14,956 ± 8,735</td>
</tr>
<tr>
<td>T3</td>
<td>1,450 ± 190</td>
</tr>
<tr>
<td>T4</td>
<td>1,706 ± 1,951</td>
</tr>
<tr>
<td>Uncoated PTFE prosthesis</td>
<td>0</td>
</tr>
</tbody>
</table>

*a G1, 10% gentamicin in PDLLA; G2, 10% gentamicin in tocopherol acetate; G3, 10% gentamicin in Softisan 649; G4, 10% gentamicin in Dynasan 118; T1, 10% teicoplanin in PDLLA; T2, 10% teicoplanin in tocopherol acetate; T3, 10% teicoplanin in Softisan 649; T4, 10% teicoplanin in Dynasan 11.*
activity, revealing a higher cytotoxic potential (10% teicoplanin in DG, in contrast, show very low metabolic activity). Prostheses coated with 10% gentamicin in DG or lower metabolic activity (32% to 67% of reference cell proliferation) and TG (77% of reference cell proliferation) followed by PDLLA (79% of reference cell proliferation), whereas teicoplanin showed a CT of 62.50 s, consistent with 10% teicoplanin in TG showed a CT of 62.50 s, whereas uncoated PTFE prostheses caused a slightly higher factor XIIa-like activity between 11.25 and 12.06 U/liter, whereas uncoated PTFE prostheses caused a slightly higher factor XIIa-like activity of 13.37 U/liter.

(ii) Amidoacyl substrate assay for factor XIIa-like activity. Assessment of factor XIIa-like activity in human blood showed that all individual coatings activated factor XIIa in the same range as uncoated prostheses. The coatings developed showed a factor XIIa-like activity between 11.25 and 12.06 U/liter, whereas uncoated PTFE prostheses caused a slightly higher factor XIIa-like activity of 13.37 U/liter.

(iii) Thromboelastography. The roTEG coagulation study provides two important parameters: clotting time (CT) and maximal clot firmness (MCF). CT describes the time interval from the start of the measurement until the initiation of clotting, whereas MCF is a dimension of the firmness of a clot. All lipid-based coatings except 10% teicoplanin in TG showed median CTs in the range of 102-146.13 s. The coating consisting of 10% teicoplanin in TG showed a CT of 62.50 s, similar to that for uncoated PTFE prostheses, 63.31 s. These data confirm the results of F1+2 assessment indicating delayed blood coagulation for almost all individual coatings. The MCFs of all lipid-based coatings are situated in the normal range of 53 to 72 mm and do not differ from those for uncoated PTFE prostheses.

(iv) Complement C3a-desArg enzyme-linked immunosorbent assay. Quantitative assessment of C3a-desArg showed different results depending on the lipid-based coating used. Prostheses coated with gentamicin sulfate incorporated into PDLLA showed very low C3a-desArg concentrations, at 189 ng/ml, whereas TA with incorporated gentamicin or teicoplanin and DG in combination with teicoplanin activated a greater amount of C3a-desArg, in a range between 406 and 441.90 ng/ml. All other coatings activated C3a-desArg fragments between 241 and 351 ng/ml, whereas uncoated prostheses caused a median C3a-desArg fragment concentration of 179 ng/ml.

**DISCUSSION**

In the present work, new anti-infective surface coatings using lipid-based drug-delivery systems were studied. The use of PDLLA, TA, DG, or TG as a carrier offers the possibility to place hydrophilic antibiotics on the surfaces of hydrophobic implants, building up a slow-release drug delivery system independent of the drug charge. Further important characteristics of individual carriers are a melting point above body temperature and the possibility of sterilization. A great diversity of antibiotics used for reasonable graft protection are described in the literature, including penicillins (18), fluoroquinolones (29), and aminoglycosides (27).

Okahara et al. (29) impregnate PTFE grafts with ofloxacin, and Prahlad et al. (31) use [14C]penicillin for antimicrobial PTFE graft protection, while Modak et al. (25) claim to achieve a less toxic and less thrombogenic effect by binding antibiotics directly or in combination with a metal such as silver to the surface of a graft; however, this method limits both the quantity of drug on the graft surface and the development of a slow drug release system.

Another way to equip grafts with anti-infective agents is to use cationic surfactants such as benzalkonium chloride (19), but cytotoxicity studies have demonstrated that these surfactants, often used as preservatives in pharmaceutical preparations, show a high cytotoxic potential even at low concentrations (9, 22), and drug choice is limited due to charge dependency.

Haverich et al. (20) and Ney et al. (27) use a fibrin sealant, while Moore et al. (26) developed a collagen release system as an antibiotic carrier for anti-infective graft protection; however, decreased hemocompatibility could result.

In this study, the coverage of a broad spectrum of pathogens was the crucial factor for antibiotics of choice. Gentamicin was chosen because it is a basic antibiotic for treating implant infections (33), whereas teicoplanin is clinically applied in more-pronounced infections and treatment of methicillin-resistant *S. aureus* (32), which is of increasing importance for nosocomial infections.

In the present work, a coating process was developed, and coated PTFE prostheses were studied in vitro for drug release, biocompatibility, anti-infective characteristics, and hemocompatibility. The reproducibility of the coating process could be ensured for TA, DG, and TG; however, the coating procedure with PDLLA showed fluctuation in terms of coating weights. The coatings developed ensure continuous drug release over 96 h and guarantee a high local antibiotic concentration around the graft. In comparison to systemic drug application, the side effects for the host organism can thereby be reduced.

Because gentamicin and teicoplanin do not dissolve in the organic solvents used, samples were coated in drug-carrier suspensions. As a result, coatings consisted of antibiotic particles incorporated into the polymer. An initial drug burst in the first hour of elution is the consequence, since antibiotic particles from the surface of the coating dissolve rapidly after con-
tact with elution buffer. Particles located deeper inside the lipid-based polymer are released only after polymer degradation or diffusion through the polymer.

In pathologically relevant bacterial concentrations, as demonstrated by Elek and Conen (11), the drug-carrier coatings developed achieved a bacterial eradication rate of 100%. This shows highly effective potency against S. aureus colonization. Even at a concentration several hundredfold beyond the maximal pathologically relevant bacterial concentration, S. aureus growth could be greatly reduced after 24 h by each of the drug-carrier coatings developed. Coatings with incorporated teicoplanin showed an insignificantly smaller growth inhibition compared with the other drug carriers. Bacterial adhesion after 24 h of incubation in a 2 × 10^6 CFU/ml S. aureus suspension could also be dramatically reduced by drug-carrier-coated prostheses compared to uncoated prostheses. Drug-carrier coatings after 24 h of drug elution did not show inhibition zones on bacterial lawns, presumably because the area of contact with agar plates was too small and drug diffusion into agar medium is not as easy as diffusion into fluid media. However, the antibacterial effects in fluid media are closer to those under physiological conditions. All coatings except DG showed small but functionally acceptable cytotoxic levels (≤22.8% decrease in cell proliferation). Tests with Oil Red O reagent show that DG is incorporated into the cell soma, apparently leading to cell death.

The hemocompatibility of individual coatings could be confirmed by several experiments. Data for activated human thrombin fragment F1 + 2 and FXIIa activity in plasma, as well as CT and MCF from roTEG tests, show that individual lipid-based coatings have an even lower thrombogenic effect than uncoated PTFE grafts. Increased C3a-desArg concentrations were caused by some of the coatings; nevertheless, tolerable C3a concentration limits have to be discussed.

Conclusions. In this study we demonstrated the development of a drug delivery system consisting of lipid-based polymers with incorporated gentamicin or teicoplanin in order to release high drug concentrations locally, in the area of implant infection. The coatings developed with PDLLA, tocopherol acetate, or Dynasan 118 as the drug carrier completely inhibited the proliferation of S. aureus in pathologically relevant concentrations while preserving biocompatible and hemocompatible characteristics. If these results can be confirmed in vivo, these drug delivery systems could be of great interest for vascular surgery.

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