Review Article

Review on Characterization, Properties, and Analytical Methods of Cefepime

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Received 26 January 2022; Accepted 24 May 2022; Published 29 June 2022

Academic Editor: Victoria F. Samanidou

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Infection is one of the most important reasons for the increase in the number of deaths worldwide; it can be a bacterial or viral infection. As a result, there are many effective drugs against this infection, especially bacterial ones. Cefepime (CP) is one of the fourth generation of cephalosporins and is distinguished from others in that it can kill both positive and negative bacteria. Therefore, this study focused on the chemical properties of the drug, its uses, and its stability against bacteria. All analysis methods for this drug in pharmaceutical preparations, blood, or plasma were also presented. One of the important problems in these methods is using toxic solvents, which poses a danger to society and the environment. The presentation of these solvents will allow companies to manufacture and use more effective and less toxic solvents.

1. Introduction

Cefepime (CP) is one of the commonly used fourth-generation cephalosporins. Cepirome and cefaclidine are other fourth-generation antibiotics. CP has adequate β-lactamase stability but with a low affinity for extended spectrum. The broad spectrum of CP is imposed to cover a wide range of positively and negatively pathogens [1–4]. Compared with ceftazidime from the fourth generation in vitro, CP has intensified activity against Gram (+) bacteria, excluding the species sensitive to methicillin, such as Streptococcus pneumoniae and Staphylococcus aureus [5, 6]. CP is more effective against extended-spectrum β-lactamase Gram (−) bacteria than other oxyimino-cephalosporins commercially available [7–9].

The cefepime’s chemical structure is displayed in Figure 1. The basic cephem ring at position 7 is modified chemically to increase the cephalosporins’ stability against β-lactamase enzymes. Similarly, other antibiotics CP such as ceftazidime, cefoperazone, cefotizoxime, and ceftriaxone from the third-generation contain a 2-amino thiazolyl acetamido group substituted with an oxyimino in the same position. However, unlike other third-generation cephalosporins, CP possesses a cephem nucleus substituted with a positively charged NMR, making it a zwitterion [2]. This zwitterionic property permits penetration of CP to Gram (+) bacteria’s porin channels rapidly [10, 11]. CP is used effectively to treat severe urinary and respiratory tract infections, as well as infections of the skin, soft tissues, and the women’s reproductive tract among patients with febrile neutropenia. Treatment of pneumonia in cystic fibrosis patients with this medication is superior to that with ceftazidime.

CP is considered an empirical monotherapy for pneumonia; it is widely used currently in hospitals for this approved indication and given to the patient with abdominal, urinary tract, febrile neutropenia, and skin or soft tissue infections. An earlier systematic published review of empirical monotherapy for the treatment of febrile neutropenia found CP to be associated with a higher mortality rate than other β-lactam antibiotics. It was unclear how the higher mortality rate was explained. CP was associated with more superinfections than other β-lactams, though the difference was not significant statistically [12]. The authors in [1] established that the overall death rate was significantly lower.
an alkoxylimino substituent. Therefore, CP has a similar gram (−) spectrum and better antistaphylococcal activity than ceftazidime [14].

4. Mechanism of Action
The E. coli porin channel penetration by CP, cefaclid, and cefpirome is at least 5–10 times faster than ceftazidime and cefotaxime. CP has stability against plasmid-mediated β-lactamase SHV-1 and SHV-2, OXA-1 and OXA-3, PSE-1, and PSE-2, and TEM-1 and TEM-2 [2]. The relative hydrolysis rates correspond to that of cefpirome [15,16], cefotaxime, latamoxef, and ceftazidime but are lesser than cepofrapone. Testing CP against 326 members of the Enterobacteriaceae found that it is more active than moxalacatam, cepofrapone, cefotaxime, cefpirome, and cepazidime. Because CP has a low empathy for the major chromosomally mediated 13-lactamase, it is probably less influenced by the nonhydrolytic barrier mechanism of bacterial resistance. CP may demonstrate to be a powerful therapy for microbial infections that are unaffected by other antimicrobials. For instance, in a new study, CP resistance rarely appeared among cefotaxime and ceftazidime-resistant Pseudomonas aeruginosa mutants [17].

5. Indications and Side Effects
The use of cefepime for treating UTIs in children has been perceived as safe and effective with the least adverse effects. Considering its broad spectrum of antimicrobial activity, it is a convenient candidate for early empiric curing of critically ill children, especially those who suffer from anatomical abnormalities of the urinary tract in which antibiotic-resistant microbes may be present less commonly [18–20] as well as infections of the skin and skin structure can be treated with CP. Besides treating bacterial infections, CP is used to cure gynecologic and intraabdominal infections, febrile neutropenia, bacteremia, meningitis, and long-term bronchopulmonary infections associated with cystic fibrosis in pediatric patients [8]. The effect of the combination of nacubactam as a β-lactamase inhibitor and CP against Escherichia coli and Klebsiella pneumonia, which are carbapenem-resistant, was reported in [21] by the authors in [22]. Cefepime is highly effective in treating COVID-19 patients with moderate and severe symptoms. Cefepime has a highly antiviral effect and is effective against large-scale viruses, including SARS and MERS. When combined with antibiotics or steroids, cefepime is considered more effective than when taken alone.

There should be a consideration for CP neurotoxicity in older patients with myoclonus who are suffering recently from alterations in mental status and renal impairment [23–26]. Seizures are the most common adverse reaction of cefepime on the central nervous system. It can also cause encephalopathy [27, 28]. Several drugs are known to cause nephrotoxicity, notably beta-lactamase inhibitors, and cephalosporins. Despite a few severe side effects, cefepime is a widely prescribed fourth-generation cephalosporin. Numerous reports suggested that cefepime may produce
| Column (C)                                      | Mobile phase                                                                 | Flow rate (ml/min) | Wavelength (nm) | Matrices                | Reference   |
|------------------------------------------------|-------------------------------------------------------------------------------|--------------------|-----------------|-------------------------|-------------|
| Supelcosil ABZ+ (5 μm; 150 × 4.6 mm)           | 20 mM PDPB pH 2: ACN (94:6, v/v, v/v).                                        | 1                  | 263             | Human serum             | [30]        |
| Hypersil BDS C18                                | Acetate buffer pH 4: ACN (97.2:2.8 v/v)                                      | 1                  | 254             | Human plasma            | [31]        |
| Hypersil BDS C18                                | MeOH: 25 mM SDPM pH 3 (87:13 v/v)                                            | 1                  | 270             | Plasma and vitreous fluid | [32]        |
| RP-C18                                         | Acetate buffer pH 3.5: MeOH/triethylamine (82:18 v/v)                         | 20 mM AA pH 4:7% ACN | 1              | Goat plasma and milk    | [33]        |
| RP Ultrasphere XL-ODS C (75 × 4.6 mm I.D.)     | MeOH: 10 mM DHP pH 7 (gradient)                                              | 1                  | 263             | Human serum             | [34]        |
| Onyx Monolithic C18 (20 cm–4.6 mm) coupled to Phenomenex C18 GC (5 cm 4.6 mm) | NaOH buffer pH 3:1 M phosphoric acid: 0.01 M n-octylamine pH 3:0:ACN         | 1.3                | 259             | Human plasma and dialysate | [35]        |
| C18 with pre-C                                  | ACN: acetate buffer (5:95 v/v)                                               | 2                  | 280             |                         | [36]        |
| μBondapak C18 (30 cm × 3.9 mm × 10 μm)         | MeOH: 40 mM phosphate buffer pH 3.2                                           | 1                  | 260             |                         | [37]        |
| Supelcosil™ LC-18 (25 cm × 4.6 mm × 5 μm), with a C18 GC | MeOH: 10 mM phosphate buffer pH 7 (25:75 v/v)                                 | 1                  | 256             | Human plasma, cerebrospinal fluid, and urine | [38]        |
| 100 × 4.6 mm i.d. Perkin Elmer phenyl C (5 μm)  | ACN (including 0.015 M pantene sulfonic acid sodium pH 3.4: glacial acetic acid and 4 with 45% KOH): water (5.5:94 v/v) | 1.5                | 280             | Aqueous solution        | [39]        |
| XTerra C18 (250 × 4.6 mm, 5 μm) supported by Phenomenex C18 GC (4 × 3.0 mm) | MeOH: sodium acetate buffer pH 6 (11:89 v/v)                                 | 1.8                | 256             |                         | [40]        |
| LiChrospher 100 RP C18 (250 mm × 4 mm, 5 μm particles) | MeOH: water (45:55 v/vv)                                                     | 0.5                | 258             | Pure and pharmaceutical dosage forms | [41]        |
| C18                                            | Acetate buffer pH 5.1: ACN: MeOH (5:20:75 v/v)                                | 1                  | 212             |                         | [42]        |
| Phenomenex ODS (4.6 × 250 mm, 5 μ)              | ACN: AA pH 4.9: (8:92)                                                       | 1.5                | 256             | Pharmaceutical formulations | [43]        |
| Acclaim 120 C18 (250 × 4.6 mm, 5 μm particle size) | MeOH: sodium acetate buffer pH 6 (11:89 v/v)                                 | 1.8                | 220             | Injections              | [44]        |
| Luna C18 (250 × 4.6 mm; 5 μm)                   | MeOH: water (45:55 v/vv)                                                     | 0.5                | 258             | Pharmaceutical dosage Form | [45]        |
| C18                                            | Water: ACN (90:10 v/v)                                                       | 1                  | 212             | CP in injections        | [46]        |
| Princeton-100 C18 (4.6 mm i.d × 250 mm., 5 μm)  | ACN: 25 mM PDPB pH 6.2 (6:9 4 v/v)                                            | 1                  | 210             | Bulk and pharmaceuticals | [47]        |
| Hypersil Gold pentfluorophenyl (PFP) 6 (2.1 by 100 mm, 1.9 μm) | 10 mM phosphoric acid                                                         | 0.5                | 260             | Human plasma             | [48]        |
| C18                                            | (ACN/0.1 M phosphoric acid/NaOH buffer pH 3): 0.01 M n-octylamine pH 3 (gradient) | 1                  | 256             | Human urine              | [49]        |
neurotoxicity, but there is no evidence that it causes acute interstitial nephritis. [29].

6. Analytical Methods for Determining CP

It is extremely imperative to quantify CP to manage bioequivalence and bioavailability studies besides pharmacokinetic parameters for curing observation. There are about 58 methods proposed for its analysis, either in pharmaceutical dosage forms, serum, or in plasma. These methods were collected from Google Scholar, PubMed, Web of Science, Scopus, and Science Direct. In this work, determination of CP by reverse phase-HPLC and HPLC, as shown in Table 1, was prevalent. With HPLC techniques, quantitative studies are characterized by the efficiency, specificity, speed, and accuracy with tracking capabilities. Table 2 contains micellar electrokinetic chromatographic methods. Some potentiometric and electrochemical methods are mentioned in Table 3, while the chromatographic technique is combined with other techniques such as LC, and HPLC. UPLC, MS, and MEKC are cited in Table 4. One of the commonly used techniques was UV absorption spectroscopy, which is used alone or with other techniques and based on colorimetry, fluorometry, and other spectrophotometric methods. All these methods are stated in Table 5. Table 6 includes gas chromatographic methods. Most of the summarized methods utilized different chemically toxic solvents as shown in all tables. Consequently, it is awfully significant for development and verification to select the analytical methods to be applied to reduce the number of toxic products. This is because it may destroy the environment, the instruments used, and the operators. To minimize such issues, it is imperative to pick an apparatus that is more specific and sensible as other, which has low costs of analysis and therefore reduces power depletion (a factor that directly affects the last price of an outcome). It needs smaller quantities of solvents or that can recognize lower concentrations, it can retrieve dangerous solvents (in order to reduce the risk of pollution in the surroundings), and it can guide pharmaceutical companies and researchers to consume nontoxic solvents and enhance the habit to decrease the risk of contamination. Hence, the analysis

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### Table 2: Micellar electrokinetic chromatographic methods for determination of CP.

| Technique       | Column (C)                      | Mobile phase or eluent                                                                 | Conditions               | Matrices                        | Reference |
|-----------------|---------------------------------|---------------------------------------------------------------------------------------|--------------------------|---------------------------------|-----------|
| MEKC            | Uncoated FSC of 50 μm           | 6 mM Na₂B₄O₇, 10 mM Na₂HPO₄, 75 mM SDS pH 9.1                                          | 257**, V of 15 kV         | Human serum and plasma          | [50]      |
| MEKC            | Uncoated FSC of 40.2 cm × 50 μm | Tris with SDS: MeOH                                                                 | 214**, V of 15 kV         | Plasma and cerebrospinal fluid  | [51]      |
| MEKC            | Uncoated FSC of 31.2 cm (21 cm × 675 mm ID) | 10 mM tris buffer pH 8.0 + 150 mM SDS and 20 mM tris buffer pH 9.0 + 200 mM SDS | 254**, V was 8 kV         | Plasma and cerebrospinal fluid  | [52]      |
| MEKC            | Bare FSC of 50 μm, 5 mmol with length 56 cm | Imidazole buffer pH 5.1                                                             | 240**, V of 25 kV         | NMP in CP for injection         | [53]      |
| MEKC            | Uncoated FSC length 31.2 cm     | Tris buffer + SDS as an electrolyte solution                                         | 214**, V of 15 kV         | Commercial injections           | [54]      |
| MEKC + indirect UV | MEKC [A 50 lm i.d. 64.5 cm (56 cm detection length) bare FSC] | MEKC (10 mM creatinine pH 3.8)                                                      | 225**                    | NMP in CP for injection         | [55]      |
| CZE             | FSC (48.6 cm × 50 μm i.d.) with 40.2 cm as a detection length 40.2 cm | 15 mm sodium borate buffer pH 9.3                                                    | 215**, V was 20 kV        | Pharmaceutical formulations and human plasma | [56]      |

* (ml/min); ** (nm).

### Table 3: Potentiometric and electrochemical methods for assay of CP.

| Technique’s name         | Solvents/Conditions                                                                 | Matrices                        | Reference |
|--------------------------|------------------------------------------------------------------------------------|---------------------------------|-----------|
| PH potentiometry         | Dilution with UB (0.1M CH₃COOH + 0.1M H₂PO₄ + 0.1M H₃BO₃)                     | Pharmaceutical preparation      | [57]      |
| Electrochemical reduction and oxidation | WE (glassy carbon electrode), RE (AgCl), AE (platinum wire) | Pharmaceutical preparation      | [58]      |
| Electrochemical Reduction | A saturated AgCl (RE), WE (dropping mercury electrode), AE (glassy carbon) PB pH 2.7 (adjusted by 1M H₂PO₄ + 1 M NaOH) | Pharmaceutical formulations and human urine samples | [59]      |
| ASV + DPP                | AE (platinum wire) For urine or plasma (PB pH 5.8), for serum (1M H₂PO₄ and 1M KOH pH 2.7) | Human urine, cerebrospinal fluid, and Serum | [60]      |
| Technique          | Column (C)                  | Mobile phase or eluent                      | Conditions | Matrices                  | Reference |
|--------------------|-----------------------------|--------------------------------------------|------------|---------------------------|-----------|
| R-HPLC-UV + (SPE)  | C18                         | MeOH: ACN : AA                            | 257**      | Nutrient admixtures       | [61]      |
| LC                 | LiChrosorb RP-C18 (250×4.6 mm I.D., 5μm particle size) | MeOH : mM monosodium phosphoric acid pH 3 (13:87 v/v) (a) 0.1% Formic acid:10 mM AA (b) 0.1% Formic acid:10 mM AA : MeOH (1:1 v/v) | 270** 1* | The bile duct microdialysis probes | [62]      |
| HILIC LC-MS/MS     | HPLC Hypersil GOLD C (150×4.6 mm, 5 μm) | (c) 2-Propanol:acetone :ACN (1:1:1 v/v/v) | Gas flow 6.5* Auxiliary gas flow 0.8* | Plasma and cerebrospinal fluid | [63]      |
| UPLC-MS/MS         | RP Acquity BEH HILIC column (50mm x 2.1 mm, 1.7 μm, Waters) | (a) (ACN) (b) 20 mM AFB (Gradient) | 0.5* | Human plasma | [64]      |
| (LC-GC-FID)        | Extraction solvent (chloroform), SGE capillary C (30m x 0.25 mm) | Water : MeOH (12 : 88 v/v) : NaCl : carbonate/bicarbonate buffer pH 5.12 | Flow rate 30* Hydrogen gas was used for the FID rate of air which was 300* | NMP in CP (pharmaceutical preparation) | [65]      |
| IC-SPE             | Metrosep C4 4 mm x 250 mm cation exchange at 30°C | 5% ACN:0.01 mM L⁻¹ nitric acid (a) ACN :25 mM AFB pH 2.79 (5:95 v/v) (b) ACN :500 mM AFB pH 2.79 +25 mM AFB (30 : 70 v/v) | 265** | NMP in CP, HCl | [66]      |
| SCX-LC/MS/MS       | Zorbax300-SCX (2.1 mm x 50 mm, 5 μm) | (a) (ACN) (b) 20 mM AFB (Gradient) | 0.5* | NMP in CP, HCl | [66]      |
| LC-MS/MS           | Luna HILIC 200A, 100 x 2.0 mm, 3 μm (Phenomenex) with a GC HPLC (Fortis reverse phase C8 (100 mm x 2.1 mm, 3 μm)) | ACN :10 mM AFB pH 3.5 (72 : 28 v/v) | 0.3* | Plasma | [68]      |
| HPLC-MS/MS         | Phenomenex (2.6μm, 100 Å, 50 x 4.6 mm) | (a) Water-formic acid:10 mM AFB (0.1 :99.9 v/v), B, MeOH | Gas flow rate, 600 l/h | Human serum | [69]      |
| VAMS-LC/MS         | Phenomenex (2.6μm, 100 Å, 50 x 4.6 mm) | (a) Water : 5 mM AA pH 5 (b) 5 mM AA in water : ACN (10 : 90 v/v) | 0.5* | Human whole blood | [70]      |
| MEKC + UV + LC/MS  | PFP Nucleodur HPLC column | Na₂HPO₄ + 75 mM pH 9.1, HPLC ((a) 5 mM AFB pH 3, (b) 100% CAN) | 254** 0.5* | Urine | [71]      |
| HPLC + MS          | RP-C18                      | ACN :10 mmol.L⁻¹ ammonium acetate (5:95) | 0.8* | Raw drug | [72]      |
should take the contribution of universities and research centers into consideration to verify the quality of drugs and their safety in application to the public.

7. Conclusions

Cefepime is one of the important drugs from the cephalosporin group as it is distinguished from the rest of the group by its resistance to bacteria, which allows it to work on many positive and negative bacterial pathogens. The drug’s stability is due to the chemical modification of its structure in the 7-position of the cephem ring, and the cephem nucleus substituted with a positively charged N-methyl-pyrrolidine, making it a zwitterion. This zwitterionic property permits penetration of the drug to Gram (+) bacteria’s porin channels rapidly, so it is used effectively to treat severe urinary and respiratory tract infections. Furthermore, many recent studies have proven its worth in treating cases of skin.

| Table 5: Spectrophotometric methods for the analysis of CP. |
|----------------|----------------|----------------|----------------|
| Technique’s name | Solvent for dissolving and dilution | Conditions | Matrices | Reference |
| DRIR + XRD | 8 ml of acetone was added as an eluent | Spectral limits 3587, 3557 cm⁻¹ | Different hydrated forms of CP.2HCl | [73] |
| FTIR | The samples were diluted to 1000 mg with KBr | 4000–400 cm⁻¹ | Pharmaceutical formulations | [74] |
| Savitzky–Golay differentiation filters and Fourier functions | Solutions prepared in concentration 100 μg ml⁻¹ in water | 266** | Human plasma | [75] |
| Complexation with Hg | Solutions were prepared in concentration 20–400 μg ml⁻¹ in water | 257** | Pharmaceutical dosage forms | [76] |
| Spectrophotometry with ammonium molybdate | Solutions were prepared in concentration 1000 μg ml⁻¹ in water | 695** | Pharmaceutical dosage forms | [77] |
| Spectrofluorometry | Solutions were prepared in concentration EXW (307), EMW (297), 435**, Dosage forms | | [78] |
| Spectrophotometry using a tetrazolium Salt | Solutions were prepared in concentration 20 μg ml⁻¹ with MeOH | 483** | Pharmaceutical dosage forms | [79] |
| UV spectrometry | Solutions were prepared in concentration Diluted with UB (0.1 M CH₃COOH + 0.1 M H₃PO₄ + 0.1 M H₃BO₃) | 264**, 230** | Pharmaceutical preparation | [57] |
| Fluorescence spectroscopy | Solutions were prepared with doubly distilled water | The fluorescent intensity set at 341** | Lysosome | [80] |
| UV + FTIR | Solutions were prepared in water; fluorescence intensity was measured in Tris/HCl solution pH 7.4 | EW was 280**, 295** | Pharmaceutical ingredient | [81] |
| Spectrophotometry | Solutions were prepared and diluted with 0.1 N NaOH | 232** | Pharmaceutical dosage forms | [82] |
| Spectrophotometry | Solutions were prepared and diluted with water | 570** | Pure and pharmaceutical dosage forms | [83] |
| Derivative spectrophotometry | Solutions were prepared and diluted with water | 239, 254 | Injections | [84] |
| Direct-infusion electrospray ionization | The solutions of NMP (N-methyl pyrrolidine) were prepared and diluted with water-MeOH (50 : 50) | ESI (V of 2000 V) flow of 71 min⁻¹, GOT of 250°C | NMP in CP | [85] |
| Microbiological assay | Powders were dissolved and diluted in water to give concentrations of 8.0, 16.0, and 32.0 μg m⁻³ | 580** | Injectable preparations | [86] |

| Table 6: Gas chromatographic methods for detection of CP. |
|----------------|----------------|----------------|----------------|
| Technique | Column (C) | Conditions | Matrices | Reference |
| GC | Wide-bore C (60m × 0.53 mm) coated with 100% polydimethylsiloxane (5 mm film) | Flow rate for CG 40, hydrogen 4 and air 100 ml/min | NMP in CP | [86] |
| | | The sample was dissolved and diluted with chloroform COT was 100°C, and the detector and the injector were 250°C | | |
soft tissues, and the women's reproductive tract among patients with febrile neutropenia either it is found to be superior in the treatment of pneumonia in cystic fibrosis patients, which drew the attention of many researchers to analyse this drug in several methods in its dosage forms or in plasma or serum, and the most common analysis methods for this drug are HPLC.

Abbreviations

**CP:** Cefepime  
**ACN:** Acetonitrile  
**NaOH:** Sodium hydroxide  
**KOH:** Potassium hydroxide  
**MeOH:** Methanol  
**PB:** Phosphate buffer  
**PDP:** Potassium dihydrogen phosphate buffer  
**SDPM:** Sodium dihydrogen phosphate monohydrate  
**C₄H₈BrN:** Tetradecyl ammonium bromide  
**GC:** Guard column  
**DHP:** Dibasic potassium hydrogen phosphate  
**AA:** Ammonium acetate  
**SDS:** Sodium dodecyl sulfate  
**MEKC:** Micellar electrokinetic chromatography  
**CZE:** Capillary zone electrophoresis  
**Na₂HPO₄:** Disodium hydrogen phosphate  
**FSC:** Fused-silica capillary  
**V:** Voltage  
**ASV:** Adsorptive stripping voltammetry  
**VAMS:** Volumetric absorptive microsampling  
**DPP:** Differential pulse polarography  
**AE:** Auxiliary electrode  
**WE:** Working electrode  
**RE:** Reference electrode  
**SPEC:** Solid-phase extraction  
**LC/MS/MS:** Liquid chromatography-tandem mass spectrometry  
**GC FID:** Gas chromatography-flame ionization detection  
**UHPLC:** Ultra-high-performance liquid chromatography  
**UPLC-MS/MS:** Ultraperformance liquid chromatography-tandem mass spectrometry  
**SCX:** High-performance hydrophilic strong cation exchange  
**HILIC LC-MS/MS:** Interaction chromatography  
**IC-CD:** Ion chromatography-conductivity detection  
**AFB:** Ammonium formate buffer  
**AA:** Ammonium acetate  
**GC:** Gas Chromatography  
**CG:** Carrier gas  
**COT:** Column oven temperature  
**NMP:** N-methylpyrrolidone  
**FTIR:** Fourier transform infrared spectroscopy  
**EXW:** Excitation wavelength  
**EMW:** Emission wavelength.

Conflicts of Interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

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