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Original Article

Analysis of peritoneal dialysis-related peritonitis pathogenic bacteria and its drug-resistance

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Abstract: Objective: Understand the pathogen spectrum changes of patients with peritoneal dialysis-related peritonitis, and provide a theoretical basis for the prevention of peritonitis, guided by a rational use of medicines in clinical treatment. Methods: Perform a retrospective analysis of the pathogen spectrum, drug sensitivity test results and disease prognosis from 76 cases, admitted to hospital in the past 6 years, of patients with peritoneal dialysis-related peritonitis. Results: Among these 76 cases of peritoneal dialysis-related peritonitis cases, the positive rate is 59.2%, with the highest proportion of gram positive cocci (71.1%), most of which are staphylococcus epidermis (26.7%). Gram positive bacteria have the highest rates of erythromycin resistance (53.1%) and are sensitive to Vancomycin. Gram negative bacteria's resistance rate of forest reaches 55.6%. Conclusion: Treatment should be based on the results of bacterial culture, with drug sensitivity tests used to select the most sensitive and effective antibiotics. We hereby recommend that empiric therapy in peritonitis can use vancomycin combined with aminoglycoside drugs. Gram negative bacteria and fungus infection peritonitis are the primary causes of patients dropping out of peritoneal dialysis.

Keywords: Peritoneal dialysis, peritonitis, drug sensitivity test

Introduction

Peritoneal dialysis is one of the methods of long-term renal replacement therapy for end-stage renal disease [1]. The device is simple, easy to operate, safe and effective. Its early survival rate is relatively high, and it can better protect residual renal function [2]. However, peritoneal dialysis is prone to infection, and has a worse effect than hemodialysis. Peritoneal dialysis-related peritonitis is the main complication of peritoneal dialysis [3, 4], which is related to increased rates of mortality and failure to follow-up with patients, and is the major cause of death or failure of peritoneal dialysis [5, 6]. Peritoneal dialysis-related peritonitis occurs with respect to a variety of factors, including dialysis procedure specification, nutrition, dialysis environment, education level and the season [7, 8]. The treatment aims to control inflammation and protect the peritoneal membrane function to the greatest degree. However, due to the heavy use of antibiotics, pathogenic bacteria's sensitivity to drugs and pathogen spectrum change constantly. Pathogen spectrum changes and the emergence of drug-resistant bacteria have brought a great deal of difficulty to the treatment of peritonitis. In this aspect, clinical microbiology and infectious diseases in European society were published in 2012 for the standard definitions of *Multi Drug Resistant, Pan Drug Resistant and Extensive Drug Resistant* of acquired drug resistant bacteria, which aimed to promote comparison of drug resistant bacteria in every medical center [9]. We conducted a retrospective analysis on the clinical information of patients with peritoneal dialysis related peritonitis from Anhui Provincial Hospital Peritoneal Dialysis Center in the past 6 years, with a statistical analysis of pathogenic bacteria and drug sensitivity test results, and a comparative analysis of bacteria spectrum and the prognosis of the disease to understand the species distribution and drug resistance of pathogenic bacteria of the center. This was done in order to provide a basis for the prevention of peritoneal dialysis-related peritonitis, to guide clinical rational drug use, improve the cure rate of peritonitis, extend the dialysis time of peritoneal dialysis patients and improve

the quality of life of peritoneal dialysis patients [10].

Materials and methods

Research materials

Target 76 patients with peritoneal dialysis-related peritonitis admitted by Anhui Provincial Hospital Peritoneal Dialysis Center from May 2008 to August 2013. This includes 43 males and 33 females, with the primary diseases including chronic glomerulonephritis with 65 (85.6%) cases, diabetes with 4 (5.3%) cases, hypertension disease with 6 (7.9%) cases, and autosomal dominant polycystic kidney disease with 1 (1.3%) case. The 76 patients include 12 cases that involve repeated recurrence, with 8 males and 6 females, and the primary diseases include 12 cases of chronic glomerulonephritis and 2 cases of hypertension. There are 32 cases of peritonitis in total in the first three years, with 17 males and 15 females, with the primary diseases including 29 cases of chronic glomerulonephritis, 1 case of hypertension disease and 2 cases of diabetes. There were 44 cases of peritonitis in the last three years, with 26 males and 18 females, with primary disease including 36 cases of chronic glomerulonephritis, 5 cases of hypertension disease, 2 cases of diabetes, and 1 case of autosomal dominant polycystic kidney disease. Except for other secondary factors causing secondary peritonitis, the selected clinical information includes the primary disease, the time of the first peritoneal dialysis, clinical symptoms, age, sex, dialysis fluid routine, pathogenic bacteria culture and the results of a drug sensitivity test. Finally, make a comparison and analysis. This study was conducted in accordance with the declaration of Helsinki.

This study was conducted with approval from the Ethics Committee of Anhui Provincial Hospital of Anhui Medical University. Written informed consent was obtained from all participants.

Diagnostic criteria for peritoneal dialysis-related peritonitis

According to the international society for peritoneal dialysis (ISPD) diagnostic criteria: (1) abdominal pain, peritoneal dialysate cloudy; (2) the count of peritoneal dialysis fluid white blood cell >100/mm^3, and multinucleated cells >50%; (3) the dialysis fluid gram stain or culture-positive. Results in line with any 2 articles of the above 3 can be diagnosed with peritonitis.

Bacterial culture and identification of bacterial species of peritoneal dialysis effluent

First, take the peritoneal dialysis effluent (peritoneal dialysis effluent at least remains in the belly for more than 2 hours) to a routine examination. Taking respectively 8~10 ml peritoneal dialysis effluent directly inoculate to a blood enrichment aerobic culture bottle and an anaerobic bottle for 16-18 h incubated in a box at 35°C. The identification of bacterial species uses the API system, so if the culture is positive, usually the result of the identification will be known after 36-72 h. If there was no bacterial growth after 5 d, then the identification will be considered to be negative. A drug sensitivity test uses the K-B disk diffusion method; the drug sensitivity test paper is purchased from Oxoid Company in Britain. The results of the drug sensitivity test are interpreted in accordance with the NCCLS and CLSI.

Judgment standard of treatment effect

After 14 h of anti-infection treatment, clinical symptoms disappear; the count of the white blood cells in peritoneal dialysis effluent is less than 100/ml. There is no bacterial growth in peritoneal dialysis effluent cultures. Within four weeks of drug withdrawal, the patient whose peritonitis cannot be relapsed is judged to be recuperated [3]. In course of treatment, the extubation turns into temporary hemodialysis because of the peritoneal dialysis effluent or the catheter removal turns into permanent hemodialysis or death. These situations are considered as treatment failure. After extubating the tube, the refractory peritonitis turns to excessive temporary hemodialysis, then re-establishing pipe and succeeds to start peritoneal dialysis, which is considered to be extubation excessive blood hemodialysis. After the refractory peritonitis extubating the tube, permanency turns into blood dialysis, which is considered as extubation permanent blood hemodialysis.

Research method

All the patients use the duplex system peritoneal dialysate manufactured by Baxter Company; all the patients are implanted by

Table 1. The composition ratio of peritoneal dialysis-related peritonitis pathogen

Pathogenic bacteria		Case (%)
Gram positive bacteria	Staphylococcus epidermidis	12 (26.7)
	Staphylococcus aureus	9 (20.0)
	Methicillin-resistant staphylococcus aureus	1 (2.2)
	Streptococcus viridans	3 (6.7)
	Mr Wolfowitz staphylococcus	2 (4.4)
	Streptococcus pneumoniae	1 (2.2)
	Enterococcus	1 (2.2)
	Micrococcus luteus	1 (2.2)
	Staphylococcus saprophyticus	1 (2.2)
	Staphylococcus hominis	1 (2.2)
Gram-negative bacterium	Pseudomonas	2 (4.4)
	Escherichia coli	2 (4.4)
	Enterobacter agglomerans	2 (4.4)
	Invasion of Pasteur	1 (2.2)
	Aeromonas hydrophila	1 (2.2)
	Lactose neisseria bacteria	1 (2.2)
Fungus	Nearly smooth white candida	3 (6.7)
	Grams of candida	1 (2.2)

Tenckhoff swan neck tube manufactured by Baxter Company. They change peritoneal dialysate for 6-8 h every day.

Retrospective analysis of the pathogen distribution, drug sensitivity test results and prognosis of disease of 76 peritoneal dialysis correlations.

Results

The positive rate and pathogenic bacteria of peritoneal dialysis effluent culture

In 76 cases of peritoneal dialysis related peritoneal dialysis effluent culture, there is a total of 45 cases of positive culture, and the positive rate is 59.2%. There are 32 cases of gram positive bacteria in pathogenic bacteria, accounting for 71.1%; among which the main is coagulase negative staphylococci. There is only one case of coagulase-positive staphylococci, accounted for 2.2%; among staphylococcus the main is staphylococcus epidermidis, accounting for 26.7%; there are only 9 cases of gram-negative bacteria, accounting for 20.0%. The proportion of enterobacter agglomerates, escherichia coli and pseudomonas are quite, accounting for 4.4% on average, among which, enterobacter agglomerates and escherichia coli belong to enterobacteria. There are 4 cases of fungus, among which, the proportion of candida parapsilosis is most frequently occurring, and there are 3 cases (3/4), shown in **Table 1**.

Drug sensitivity test results of the peritoneal dialysis related peritonitis pathogens

Drug-fast of the peritonitis pathogens is shown in **Table 2**. In gram positive bacteria, the highest drug resistance rate is in the oxacillin and erythromycin, which reach 52.9%. It also has a high drug resistance rate in gentamicin and penicillin G, which respectively are 47.8% and 47.1%; it is sensitive to vancomycin. In gram negative bacteria, the highest drug resistance rate is cefazolin, which reaches 55.6%; there follows ampicillin, in which the drug resistance rate is 33.3%. There is no resistance to ciprofloxacin, ceftriaxone, cefotetan, or imipenem.

The prognosis of peritonitis

There are 76 cases, among which there are 60 patients who have been cured (78.9%), there are 12 cases of extubation (15.8%) turning to hemodialysis, and there are 4 cases of death (5.3%). There are 5 cases of repeated relapse (35.7%), there are 5 cases of extubation (35.7%) turning to hemodialysis, and there are 4 cases of death (28.6%). Among the 32 cases of gram-positive bacterial infections patients, there was only one case of death, and 2 cases of extubation turning to hemodialysis. Among the 4 cases of fungal peritonitis, there are 3 cases of extubation, one of which was cured. There are 14 cases of repeated relapse patients, there are 9 cases of twice relapsed patients, 2 of which have died, 2 of them have turned to hemodialysis, and 5 cases were cured. There are 5 cases of triple relapse patients, 2 of whom died, 2 of them turned into hemodialysis, and 1 case of subcutaneous fungal infection

Table 2. Drug resistance rate of peritoneal dialysis-related peritonitis pathogen

Pathogenic bacteria	Drug	Persister	Intermediary	Sensitive strains	Drug-resistant percentage
Gram negative bacteria	Amikacin	0	0	9	0
	Ampicillin	3	3	3	33.3%
	aztreonam	1	2	6	11.1%
	ceftazidime	0	1	8	0
	Ciprofloxacin	0	0	9	0
	ceftriaxone	0	0	9	0
	cefazolin	5	0	4	55.6%
	Cefotetan	0	0	9	0
	Ampicillin/sulbactam	1	1	7	11.1%
	Imipenem	0	0	9	0
Gram positive bacteria	Penicillin G	13	6	13	40.1%
	Vancomycin	0	0	32	0
	Oxacillin	15	0	17	46.7%
	rifampicin	0	2	30	0
	Clindamycin	4	0	28	12.5%
	Erythromycin	17	0	15	53.1%
	levofloxacin	4	2	26	12.5%
	Gentamicin	9	0	22	28.1%
	Tetracycline	9	0	22	28.1%
	Ampicillin	4	6	22	12.5%

Table 3. The constituent ratio of prognosis (%) = the case number of prognosis/the total case number of each pathogen

	Cases	Death	Pull tube to hemodialysis	To become better
Gram positive bacteria	32	1 (3.1)	2 (6.2)	29 (90.6)
Gram negative bacteria	9	1 (11.1)	2 (22.2)	6 (66.7)
Fungus	4	0 (0)	3 (75)	1 (25.0)
Culture negative bacteria	31	2 (6.5)	5 (16.1)	24 (77.4)

patient improved after taking the antifungal therapy and then kept going on the peritoneal dialysis. All kinds of prognosis of peritonitis caused by pathogenic bacteria are shown in **Table 3**. The prognosis of repeated relapse patients is shown in **Table 4**.

The cases are divided into 2 groups: one includes cases from 2008 to 2010, and the other includes cases from 2011 to 2013. The bacteria spectrum and disease prognosis of the groups are compared. The proportion of gram positive bacteria in the first three years was 50% and 36.2% in the second three years; the proportion of gram negative bacteria in the first three years was 9.4% and 13.6% in the second three years, which shows a tendency towards growth. The improvement rate of gram positive and gram negative bacteria after treatment were both 100% in the first three years and the improvement rate of culture negative peritonitis after treatment was 81.8%. The improvement rate declined in the second three years. However, cases of fungal infection are rarely seen in these files, which mean the difference between the two groups has no statistical significance. However, the results remind us to pay more attention to the emergence of fungal resistance. This change of disease prognosis is considered mostly related to the emergence of drug-resistant bacteria. See **Tables 5**-**7**.

Discussion

So far, continuous quality improvement (CQI) has been the main approach to decreasing peritonitis infection rate in peritoneal dialysis centers and an important method to managing a dialysis center. Guided by the peritonitis treatment of 2010, regular review of pathogenic bacteria, drug susceptibility and possible reasons that can lead to peritonitis have been emphasized, to enable immediate intervention

Table 4. The constituent ratio of prognosis (%) = the case number of prognosis/the total number of cases with different recurrence times

Recurrence times	The number of cases	Death	Pull tube to hemodialysis	To become better
1	43	1 (2.3)	5 (11.6)	37 (86.1)
2	9	2 (22.2)	2 (22.2)	5 (55.6)
3	5	1 (20.0)	3 (60.0)	1 (20.0)

Table 5. 2008~2010 and 2011~2013 Comparison of bacterial spectrum

	Gram positive bacteria	Gram negative bacteria	Gram negative bacteria	Culture negative
2008~2010	16 (50.0)	3 (9.4)	2 (6.3)	11 (34.4)
2011~2013	16 (36.2)	6 (13.6)	2 (4.5)	20 (45.5)

Table 6. The constituent ratio of prognosis (%) = the case number of prognosis/the total case number of each pathogen

	The number of cases	Death	Pull tube to hemodialysis	To become better
Gram positive bacteria	16	0 (0)	0 (0)	16 (100)
Gram negative bacteria	3	0 (0)	0 (0)	3 (100.0)
Gram negative bacteria	2	0 (0)	1 (50.0)	1 (50.0)
Culture negative	11	0 (0)	2 (18.2)	9 (81.8)

Table 7. 2011~2013 Outcome of peritonitis (n (%))

	The number of cases	Death	Pull tube to hemodialysis	To become better
Gram positive bacteria	16	1 (6.7)	2 (13.3)	12 (80.0)
Gram negative bacteria	6	1 (16.7)	2 (33.3)	3 (50.0)
Fungus	2	0 (0)	2 (100.0)	0 (0)
Culture negative	20	2 (10.0)	3 (15.0)	15 (75)

in the circumstances of high infection rate. The cultivation results of pathogenic bacteria of CAPD-related peritonitis in our peritoneal dialysis center shows the negative rate of 38.2%, unable to reach the fact that the proportion of culture negative peritonitis of all peritonitis cases should not be more than 20%, but identical with the report [11]. The information of this research shows that some patients are suffered from peritonitis repeatedly. Some foreign reports shows that the incidence of peritonitis is not only related to a patients' immune situation, but also related to many factors such as whether the operation is standard, aseptic concept, age, gender [12], education level, changes of pathogenic bacteria and the environment [13]. Yang Jun [14] *et al*. conducted retrospective analysis on clinical data of 136 CAPD-related peritonitis and figured out that the incidence of peritonitis was not only related to the factors mentioned above, but also closely related to patients' nutritional status, morbidity seasons, and the number of follow-ups within one year. However, in the research of the relationship between underlying diseases and the incidence of peritonitis, cases of peritonitis among diabetic patients are slightly more prevalent than in non-diabetic patients, but it shows no significant difference and the incidence of peritonitis showed some relationship with the insulin added into the peritoneal dialysis fluid, which also conforms to the foreign reports [12]. Although we don't have many diabetic patients in our peritoneal dialysis center, none of the diabetic patients suffered from peritonitis repeatedly, which conforms to foreign reports as well [13, 14]. Therefore, subcutaneous injection of insulin is recommended for diabetic patients and adding insulin into dialysis fluid should be avoided so as to reduce the chance of contamination. Our center adopts the method of intraperitoneal administration of first generation cephalosporin combining with third generation cephalosporin which is recommended in the ISPD guide as the experiential treatment plan. For patients suffering from infection recurrence and relapse, antibiotics were chosen according to drug susceptibility results of last time. Most patients' peritoneal dialysis fluid turned clear after 3 days' treatment, while a few patients' drugs needed adjusting according to the susceptibility results and the cure rate of peritonitis was 80.6%. If the peritonitis was not able to be controlled after 5 days' treatment, it shall be diagnosed as refractory peritonitis and doctors shall consider removing the peritoneal dialysis catheter. From this fact, we

can see the significant importance of initial experiential administration. With the spread of antibiotics and improvement of peritoneal dialysis techniques, the pathogenic bacteria spectrum of CAPD-related peritonitis changed dramatically. Huang [15] *et al*. conducted retrospective analysis on the change of the pathogenic bacteria spectrum of CAPD-related peritonitis in the last 26 years. The research showed that gram positive bacteria was still the main pathogenic bacteria, yet the proportion of gram negative bacteria increased up to 25.9%. The pathogenic bacteria spectrum in our peritoneal dialysis center showed the same changes.

Now the pathogenic bacteria spectrum in our peritoneal dialysis center promotes its remaining gram positive bacterial infections based on the identical facts in the report. Combined with multiple research results, it is suggested that during the anti-infection, we should pay attention to the possibility of gram negative bacterial infections. The main pathogenic bacteria of the center is gram positive coccus (accounting for 71.1%), including 26.7% of staphylococcus epidermises taking the highest percentage. Staphylococcus epidemidis often colonizes a human's nasal cavity, oral cavity, fingernail, skin and so on, so we shall consider that it is closely related to the cause of peritonitis and misoperation, and lack of awareness of aseptic operation. Except when the bacterial invades the enterocoelia through the peritoneal dialysis catheters or its surrounding, blood stream infection and retrograde infection, another important pathogenesis of the peritonitis is the intestinal bacteria metastasizing into enterocoelia. Recent research demonstrates that astriction, hypokalemia, colonoscopy and gynecologic examination [16, 17] can increase the risk of the intestinal bacteria heterotopia into enterocoelia like the pathway and it is also the reason why the gram-negative bacteria caused peritonitis occupies a certain proportion. Fungal infection is uncommon in the data, accounting for 8.9% of all peritoneal dialysis-related peritonitis which is identical with the report [18]. The statement of pulling out the peritoneal dialysis catheters shall obviously promote the prognosis of fungal peritonitis having been proved again in the peritoneal dialysis center. We have 4 cases of fungal peritonitis, three of which involve the pulling out of the catheters and changing into hemodialysis and one of them is the fungal infection of a subcutaneous tunnel which was given the treatment of anti-infection and continued formal peritoneal dialysis after it became better. It also further proved the important function of the treatment of fungal peritonitis. Compared with bacterial peritonitis, fungal peritonitis has a higher dropout rate (75.0%). Research has shown that [19] the use of antibiotics is the most common predisposing factor which leads to fungal peritonitis. In this research, there are 31 cases of culture negative which accounts for 40.8% and it can't reach the requirements of fewer than 20% of the ISPD (International Society for peritoneal dialysis). The reasons why the culture negatives have been given detailed analysis before, here no longer to say. During the treatment of the culture negative peritonitis, combined with the treatment recommendation in 2010 and the pathogenic bacteria, drug resistance in the dialysis center to give a primary empirical anti-infectious treatment scheme which has a 66.7% improvement rate, lower than the gram positive bacterial peritonitis and gram negative bacterial peritonitis, and higher than fungal peritonitis. It has proved again the importance of primary empirical anti-infectious treatment. But how to change antibiotics when the empirical treatment and culture negative peritonitis treatment are ineffective? Research has proved that the pathogenic bacteria of a majority culture negative peritonitis are gram positive bacterial by the means of testing endotoxin of patient through LAL. So when it is ineffective after 3 days' primary empirical anti-infectious treatment, we shall consider further strengthening the force of anti-gram positive bacterial infections. In the research, we divided the whole case into two parts by time to compare the variation of pathogenic bacteria and the variation of outcomes of the disease in our center. Research shows that the pathogenic bacteria in our center is changing, the occupation of gram positive bacterial decreases is from 50% to 36.2%, the occupation of gram negative bacterial increases from 9.4% to 13.6%, but now gram positive bacterial is still the main source. Because of the small number of fungal peritonitis, the variation of the incidence of fungal peritonitis has no statistical significance. The cure rate of the gram positive bacterial and the gram negative bacterial of peritonitis are respectively decreased from 100% to 80% and 100% to

50%. In particular, the cure rate of the gram negative bacterial decreases from 100% to 50% and it shows the increase of drug resistance of gram negative bacterial. Some foreign research shows the reason for the production and exacerbation of drug-resistance bacteria is considered as the result of a drug or some drugs served as the first-line drugs for a long time [20].

The result of the research proved that the gram positive bacteria in our center has no resistance to vancomycin but it has a high resistance to oxacillin, erythromycin, gentamicin and penicillin G, so we shall consider giving the vancomycin primary empirical anti-infection treatment. Several dialysis centers in China have been saving vancomycin as the initial medicine for empirical treatment [21]. Aminoglycoside antibiotics may have an influence on the survival of renal function, but yiduo center has found that use aminoglycoside antibiotics inside enterocoelia have no influence on the survival of renal function [22]. An Australian peritoneal dialysis center has been extensively used to treat of peritonitis because of the advantages of its economical, broad antibiotic spectrum and post antibiotic effects [23]. Our dialysis center uses the first generation cephalosporin combined with the third generation cephalosporin to dose intra-abdominal as always, as a single does one day and the medicines should dwell more than 6 hours. According to the proposition "individualization of center" of the initial treatment of antibiotics and combined with the result of the research, it suggests the adjustment of the initial treatment to vancomycin combined with the third generation cephalosporin. As for the serious systemic symptoms shown by patients we can give a dose of intravenous systemic. As for the treatment, the use of antibiotics is sufficient and the use of the relatively simple antibiotics of peritonitis should last for 2 weeks. As for the complex peritonitis (such as colibacillus, staphylococcus aureus, etc.), the use of antibiotics should last for 3 weeks; for the refractory peritonitis, it should be pulled out of the peritoneal dialysis catheter in time to protect peritoneal function. After 2~3 weeks of the control of infection the catheterization for peritoneal dialysis should be continued. All of above-mentioned are in order to decrease the drug-resistance bacteria, the development of refractory peritonitis or improve the cure rate of refractory peritonitis. As for the treatment of fungal peritonitis, this handout doesn't do specific drug sensitivity analysis, which is also a shortcoming of the research and it will be further improved in future studies. Combined with 2010 SPD guidelines, you can choose the combination of flucytosine and amphotericin as initial treatment.

Conclusion

It should strengthen the education of the relevant knowledge. According to recent research, gram positive bacteria is still the main pathogenic bacteria which leads to peritoneal dialysis-related peritonitis, but the proportion of gram negative bacteria has a growth trend. Gram positive bacterial has a high drug resistance to oxacillin and erythromycin, so it is not suitable for routine empirical antibiotics; when we use antibiotics we strictly control the indication and therapeutic principle of antibiotics. Regular detection of the test status of pathogenic bacteria and drug susceptibility is in order to prevent the development of extended-spectrum drug-resistance bacteria. Due to the limited number of cases, partial results can't reflect real situation more specifically. The research will be further improved on the basis of the expansion of medical records.

Disclosure of conflict of interest

None.

Authors' contribution

Wei Ren Substantial contributions to the conception and design of the work; the acquisition, analysis, interpretation of data for the work; Lei Lan and Yan Jin drafting the work and revising it critically for important intellectual content; And Yuan Fang final approval of the version to be published; Wei Chen and Peng Wang agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

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