

Meta-Analysis of the Efficacy of Cimetidine in the Treatment of Mumps

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Abstract: *Objective:* To compare the efficacy of cimetidine and ribavirin in the treatment of mumps by meta-analysis. *Methods:* Controlled trials of cimetidine and ribavirin in the treatment of mumps were searched through China National Knowledge Infrastructure (CNKI), Wanfang data, Cqvip, Pubmed, The Cochrane Library and EMBase databases up to September 2022. The effective rate, the time of swelling regression in parotid gland area and the rate of adverse reactions were analyzed by Review Manager 5.3 software. *Results:* The final 10 articles included 920 children, including 427 in the trial group and 447 in the control group. Meta analysis showed that the effective rate of cimetidine in the treatment of mumps was higher than that of ribavirin in routine treatment, with a statistically significant difference (odds ratio [OR] = 5.2, $P < 0.00001$); The time of swelling regression was statistically significant (OR = -1.28, $P < 0.00001$); The difference of adverse reaction rate was not statistically significant (OR = 0.73, $P = 0.62$). *Conclusions:* Compared with ribavirin, cimetidine is more effective in the treatment of mumps, with shorter swelling regression time without increases of adverse reactions.

Keywords: Cimetidine; Ribavirin; Mumps; Meta-analysis

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1. Introduction

Mumps is an infectious and self-limiting acute respiratory disease characterized by swelling and pain in the parotid glands centered on the bilateral earlobes^[1,2]. The commonly used treatment methods are antiviral therapies and combination of traditional Chinese and Western medicine. Cimetidine, also known as Tagamet, is a histamine H₂ receptor antagonist, and is a commonly used gastric acid inhibitor and anti-ulcer drug^[3]. In recent years, studies have shown that it has an immunomodulatory effect, which can reduce the susceptibility of infectious diseases, and has certain value in anti-virus and anti-tumor immunotherapy^[3-5]. Meta-analysis is an analytical method of evidence-based medicine. It is a research method that systematically and comprehensively analyzes multiple independent research results with the same objective and makes the best use of existing data. It is a statistical method as well as an observational study in itself, and also follows the basic principles of scientific research. Meta-analyses are suitable for proposing the importance of the combined or related effects of new treatments, providing the best treatment option in comparing different treatments, and measuring the degree of stability of treatment^[6].

At present, although there are reports on the use of cimetidine in the treatment of mumps, there is a certain bias due to the influence of sample size, region, objects and other factors. In order to further understand the efficacy of cimetidine in the treatment of mumps, a meta-analysis was conducted in this study on the efficiency, swelling regression time and rate of adverse reactions, in order to provide a

reference for clinical drug use.

2. Materials and methods

This study followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines) and the Cochrane Handbook.

2.1. Research subjects included in the literature

2.1.1. Inclusion criteria

The research type is a controlled trial, which is not limited by language and publication where the research subjects are patients diagnosed with mumps (parotid gland swelling and pain, fever, elevated blood amylase). The treatment methods are as follows: the experimental group used cimetidine, while the control group received ribavirin conventional antiviral therapy; the dosage, mode of administration, and course of treatment were not limited; the primary outcome was the effective rate, and the secondary outcome was the rate of adverse reactions/complications, and the time of regression of parotid gland swelling. On the basis of having the same efficacy, the rate of effective rate = number of effective cases/total number of cases × 100%, and rate of adverse reactions = number of adverse reaction cases/total number of cases × 100%.

2.1.2. Standard of effective rate

Disappearance of clinical symptoms such as fever, swelling and pain in the parotid gland area, and a good mental state.

2.1.3. Symptoms of adverse reactions

Diarrhea, abdominal distension, bitterness, dry mouth, mild elevation of serum transaminases, and so on.

2.1.4. Exclusion criteria

There are serious errors in the research data, and the original text cannot be obtained; the quality of the research is poor; the first article is reserved for the repeated publication, and the one with the most complete data is reserved for the repeated data.

2.2. Search strategy

Chinese databases: CNKI and Wanfang Data knowledge service platform. Foreign language databases: PubMed, Cochrane Library, and EMBase. The retrieval time is from the establishment of the database to September 2022. The Chinese search terms were “流行性腮腺炎(mumps),” “西咪替丁(cimetidine)” and “甲氧米胍(tagamet),” at the same time, gray literatures such as dissertations and conference papers are also retrieved; the English search terms were “mumps and cimetidine”, and a comprehensive search of subject terms combined with free words was carried out in combination with the respective characteristics of the database. A total of 175 literatures were retrieved. After eliminating duplicates, irrelevant literatures, those without full abstracts or texts, traditional Chinese medicine research or combination therapy, selecting clinical studies, excluding descriptive results, 18 literatures that use cimetidine for the experimental group and use ribavirin for the control group were selected, as shown in **Figure 1**.

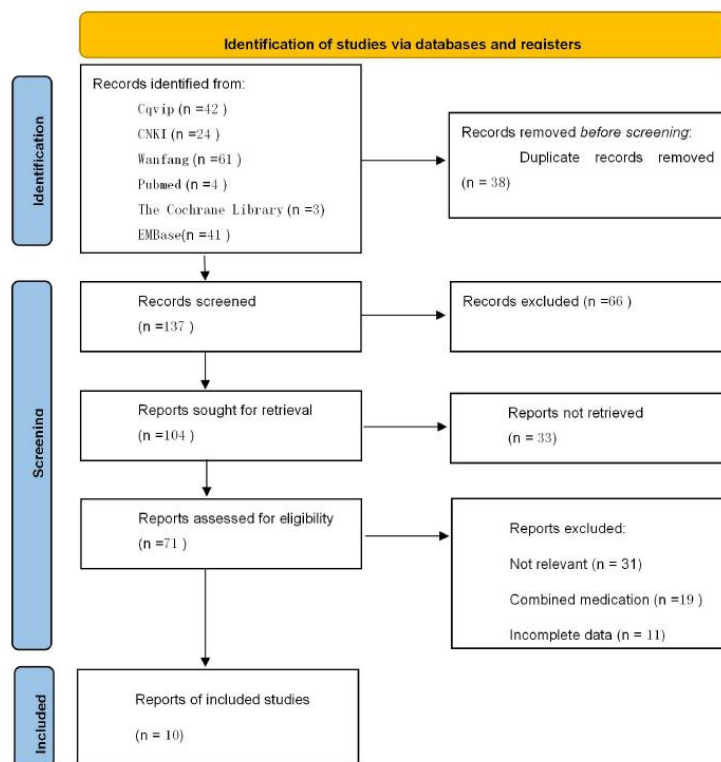


Figure 1. PRISMA flow chart of study selection for systematic review

2.3. Literature quality evaluation and extraction

Literature screening: Two researchers independently screened the literature according to the screening criteria. For the literature that was difficult to determine whether to be included, it was resolved through discussions or through the evaluation of a third party. Firstly, the initially screened literature was imported into EndNote for duplication check. Then, the title and abstract of the literature for preliminary screening were read, and literature that clearly did not meet the inclusion criteria were excluded. The full text of the selected literature were the rescreened to determine those that can be used for these study. The main evaluation index was the effective rate and the secondary evaluation indexes were swelling regression time and adverse reaction rate, which were performed using meta-analysis.

2.4. Data analysis methods

Meta-analysis was performed using Review Manager 5.3 software. Evidence strength analysis was performed using GRADEprofiler 3.6 software.

3. Results

3.1. Literature search, quality evaluation and inclusion

18 relevant literatures were selected through preliminary search, and the full texts were included for further screening. Finally, 10 literatures [7-16] that met the criteria were included for meta-analysis, all of which were Chinese. Among them, 920 children were included, including 427 in the trial group and 447 in the control group. The effect of cimetidine and ribavirin treatments were compared in all of the papers, with the trial group using cimetidine, and the control group was using ribavirin. Among them, 8 literatures reported the effective rate, 2 literatures reported adverse reactions, and 5 literatures reported the time of clinical symptoms regression, and the study baseline was balanced. As can be seen from **Figure 1**, among

the 10 literatures selected in this meta-analysis, 2 did not mention randomization, 6 mentioned randomization (one of them mentioned randomization method), and 2 did not adopt randomization method; allocation concealment, blinding and blinding methods were not mentioned in all 10 literatures; the results of the 10 articles were all complete, with no selective reporting and no other biases. The quality of the literature can be seen in **Figure 2**.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bian Z2017	+	-	-	-	+	+	+
Chan Q2012	+	-	-	-	+	+	+
Chen C2016	-	-	-	-	+	+	+
Chen L1995	-	-	-	-	+	+	+
Huang G2008	-	-	-	-	+	+	+
Le J2000	+	-	-	-	+	+	+
Liu X2016	+	-	-	-	+	+	+
Mao S2003	+	-	-	-	+	+	+
Shi J2017	+	-	-	-	+	+	+
Sun L2015	-	-	-	-	+	+	+

Figure 2. Methodological quality of included documents

3.2. Meta-analysis of effective situations

The results of meta-analysis using random effect model showed that the cimetidine is more effective than ribavirin in treating mumps, and the difference was statistically significant (odds ratio [OR] = 5.2, 95%CI [2.98, 9.05] , $P < 0.00001$). It can be seen from **Figure 3** that the OR values of the different studies are not far apart and $I^2 = 0\%$, indicating that the literature is highly homogenous. The diamond in the figure is located on the right side of the invalid line and the combined OR = 5.20 of the effective rate of treatment is greater than 1, showing that the effective odds ratio of cimetidine in the treatment of mumps is higher than that of ribavirin, which means that the effectiveness of cimetidine is higher than that of ribavirin.

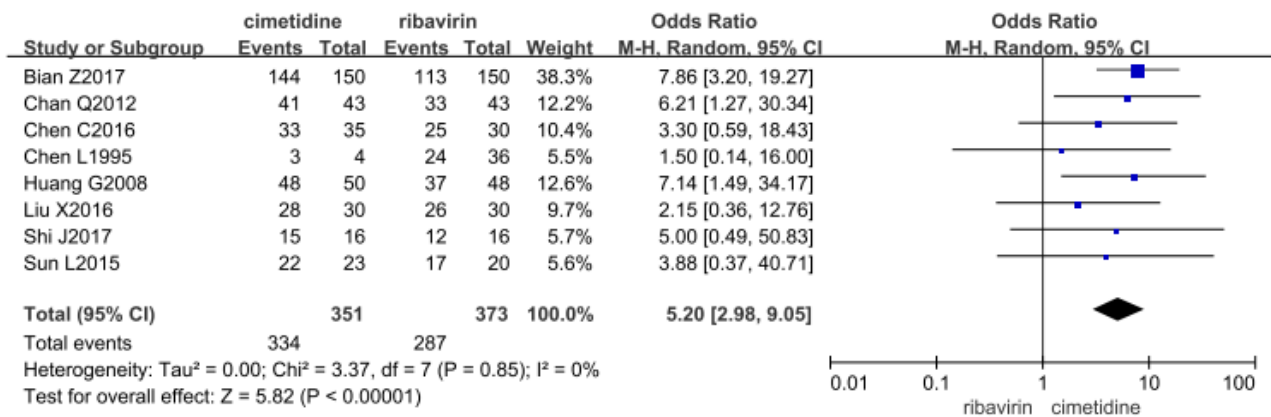


Figure 3. Effective rate of cimetidine versus ribavirin in the treatment of mumps

Table 1 shows that the strength of evidence in this evaluation is moderate, and further literature is needed to support the results.

Table 1. Strength of evidence of effective rate of cimetidine versus ribavirin in the treatment of mumps

Cimetidine vs ribavirin in the effective rate for mumps						
Patient or population: patients with mumps						
Settings:						
Intervention: Cimetidine vs ribavirin in the effective rate						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Cimetidine vs ribavirin in the effective rate				
The effective rate Follow-up: 10 days	Study population		OR 0.19 (0.11 to 0.34)	724 (8 studies)	⊕⊕⊕⊕ ¹ moderate ¹	
	952 per 1000	789 per 1000 (684 to 870)				
	Moderate					
	948 per 1000	776 per 1000 (667 to 861)				

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

¹ No explanation was provided

3.3. Meta-analysis of swelling regression time

The results of meta-analysis using random effects model showed that the swelling regression time of cimetidine treatment of mumps was shorter than that of ribavirin conventional treatment, and the difference was statistically significant (OR = -1.28, P < 0.00001), as shown in **Figure 4**. Besides, the OR values are not far apart and I²=37%, indicating that the literature is highly homogenous. The diamond in the figure is located on the left side of the invalid line and the combined OR = -1.28 value of swelling regression time is less than 1, indicating that the odds ratio of swelling regression time in the treatment of mumps using cimetidine was lower than that of ribavirin and was negative, which means that the time of cimetidine swelling regression was shorter than that of ribavirin.

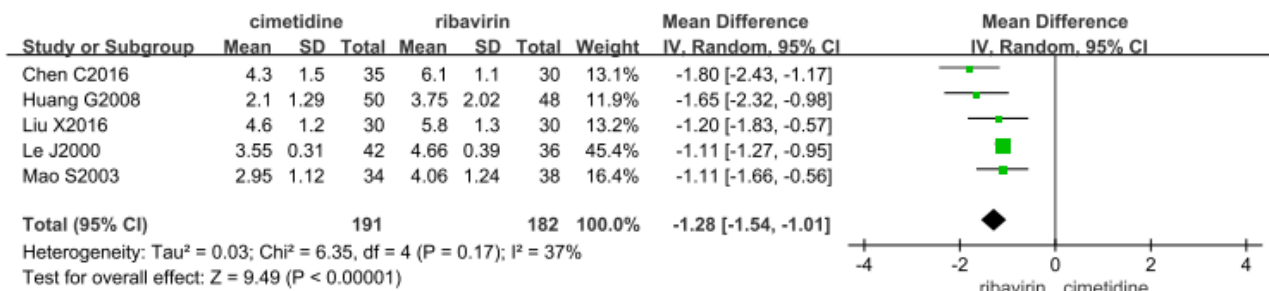


Figure 4. The time of swelling regression of cimetidine versus ribavirin in the treatment of mumps

Table 2 shows that the strength of evidence in this evaluation is moderate, and further literature is needed to support the results.

Table 2. Strength of evidence of the swelling regression time of cimetidine versus ribavirin in the treatment of mumps

Cimetidine vs ribavirin in the time of swelling regression for mumps						
Patient or population: patients with mumps						
Settings:						
Intervention: Cimetidine vs ribavirin in the time of swelling regression						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Cimetidine vs ribavirin in the time of swelling regression				
The time of swelling regression Follow-up: 10 days		The mean the time of swelling regression in the intervention groups was 1.28 higher (1.01 to 1.54 higher)		373 (5 studies)	⊕⊕⊕⊕ moderate ¹	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval;
 GRADE Working Group grades of evidence
 High quality: Further research is very unlikely to change our confidence in the estimate of effect.
 Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
 Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
 Very low quality: We are very uncertain about the estimate.

¹ No explanation was provided

3.4. Meta-analysis of the incidence of adverse reactions

Meta-analysis using random effects model showed that the adverse reaction rate of cimetidine in the treatment of mumps was not higher than that in ribavirin conventional treatment, and the difference was not statistically significant (OR = 0.73, 95%CI [0.21, 2.58], P = 0.62), as shown in **Figure 5**. It can be seen from **Figure 5** that the OR values are not far apart and I² = 0% indicates that the literature is highly homogenous. The intersection of the diamond and the invalid line in the figure indicates that there is no difference in the adverse reactions of cimetidine compared with ribavirin.

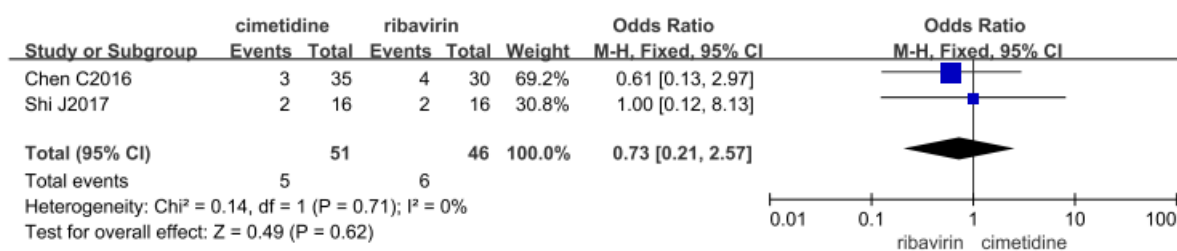


Figure 5. Analysis of adverse reactions of cimetidine versus ribavirin in the treatment of mumps

Table 3 shows that the strength of evidence in this evaluation is moderate, and the results need further literature support.

Table 3. Strength of evidence of adverse reactions of cimetidine versus ribavirin in the treatment of mumps

Adverse reaction rate for mumps						
Patient or population: patients with mumps						
Settings:						
Intervention: adverse reaction rate						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Adverse reaction rate				
The adverse reaction rate Follow-up: 10 days	Study population		OR 1.37 (0.39 to 4.83)	97 (2 studies)	⊕⊕⊕⊕ moderate ¹	
	98 per 1000	130 per 1000 (41 to 344)				
	Moderate					
	105 per 1000	138 per 1000 (44 to 362)				

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

¹ No explanation was provided

4. Discussion

It can be seen from the results that compared to the currently commonly used ribavirin, cimetidine is more effective in the treatment of mumps, with faster swelling regression and similar adverse reactions. However, in the study of effectiveness, the OR value confidence interval of 5 literatures crossed the futility line, and only 2 literatures reported on adverse reactions, making the strength of the evidence is medium, which needs to be further demonstrated.

In addition, this study also has certain limitations: the included studies are all from China, and the generalizability of the findings may be low; none of the included studies mentioned the use of blinding or allocation concealment, thus there may be implementation bias, measurement bias and selection bias. The uncertainty about the risk of bias also affect the objectivity of the research results. Although most of the articles mention random assignment, the randomization method is not described in detail, and there are certain risks; the sample size of the included studies is small, and the representativeness of the target population is not strong. It is expected that there will be more large-scale and more rigorous studies.

Mumps is an infectious disease caused by the mumps virus. Spring and winter are the high-incidence seasons, and children aged 3-14 are the most disease-prone population. Our country is a country with a relatively high incidence of mumps [1,17]. Although the disease is self-limited, it tends to attack the glands and is also neurotropic, and may cause complications like viral meningitis, pancreatitis, orchitis, deafness, and permanent nerve damage [18]. The disease is a Class C infectious disease in our country. Since the 1960s, our country has started to use the mumps vaccine to prevent this disease and has achieved great results [19]. Since there is only one serotype of the virus, it means that people who have been sick or vaccinated should theoretically be immune for life, but in clinical work, we have found that there are also cases of infection even after getting the vaccine. This may be related to the limited antigenic crossover between different genotypes which causes the same vaccine to produce different protective effects against different genotype strains [20-22]. As of now, 12 genotypes have been found in the world, of which 2 are the main epidemic strains in China [20, 21]. There are differences in the geometric mean concentration of antibodies among people of different ages, regions, whether the mumps vaccine was taken, and lower

antibody titers may also lead to a re-infection ^[22]. In this study, the possibility of replacing ribavirin with cimetidine as a mumps treatment drug was investigated. It has a high effective rate, shorter swelling regression time and similar adverse drug reactions to ribavirin, so it can be regarded as a new method of treatment.

The possible mechanisms of treatment of mumps using cimetidine are as follows: improves the transformation rate of T lymphocytes, increases the secretion level of interleukin 2 (IL-2) in the body, and enhances the immunity of sick children ^[23]; controls the production of histamine, reducing capillary permeability and inhibits edema ^[23]; effectively blocks the activity of histamine on suppressor T cells, thereby enhancing the body's immune response; activates Th1 cell immune function and plays a role in antiviral infection ^[4]; directly acts on mast cells to inhibit the secretion of inflammatory mediators, thus promoting inflammation regression; they can also indirectly inhibit the release of cytokines to reduce systemic inflammatory responses ^[24]. For the treatment of mumps, cimetidine can exert its anti-virus, swelling, pain-relieving effects, significantly reduce swelling and pain caused by the disease, shorten the course of the disease and relieve the pain of children.

In order to generate high-quality evidence to guide the use of cimetidine in the treatment of mumps, some suggestions for future related clinical research are made: standardization that are in accordance to the latest diagnostic guidelines in the program design stage, strict inclusion and exclusion criteria, are needed to obtain a recognized efficacy evaluation; record adverse drug reactions, as they are also important indicators for determining drug efficacy; the specific procedure of the randomization methods need to be recorded in detail, as randomized controlled trials are the gold standard for clinical research, thus it should be well-designed to ensure the effective conduct of the randomized trial; records of the use of blinding in detail. This is because randomization is the only way to prevent implementation bias and measurement bias, therefore, emphasis should be given to the use of blinding and recording of relevant conditions; the allocation concealment should be recorded, so that the probabilities of patients entering the experimental and control groups are equal; in existing studies, the sample size is generally small, which will inevitably cause bias. Therefore, it is expected that there will be studies with large sample sizes.

In addition, in the process of reviewing the literature, the domestic literature focuses on the treatment of mumps using cimetidine while foreign literature focuses on using cimetidine in the treatment of papillomavirus. There are 3 articles about mumps in Cochrane Library, namely vaccination, traditional Chinese medicine and acupuncture. It can be seen that traditional Chinese medicine treatment of mumps is very distinctive and is also a leading treatment method. Hence, further research should be done on the treatment of mumps with traditional Chinese medicine and acupuncture in the future.

5. Conclusion

In conclusion, based on the existing data and methods, cimetidine is more effective than ribavirin in the treatment of mumps, with shorter swelling regression time and a similar rate of adverse reactions. However, due to the relatively small number of literatures that can be included and the low quality of literatures, the research results need to be further verified. It is recommended to design a randomized controlled study with a large sample size, multi-center, and standardized trials to improve the reliability of the evidence, and then study the efficacy and safety of cimetidine in the treatment of mumps, in order to provide more reliable information and evidence for the clinical use of the drug

Disclosure statement

The authors declare no conflict of interest.

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