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Efficacy of Orally Administration of Banxia Houpu Tang With Low Dose of Angiotensin-Converting Enzyme Inhibitor（ACEI）for Preventing Pneumonia Risk in Older Adults With Dementia －Case Reports－

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Pneumonia is a major cause of mortality and morbidity, particularly among those who are older and debilitated. Pneumonia is not only a common infection in elderly people, but is also the most common cause of death in this population. It has been said that marked depression of swallowing and cough reflexes induce aspiration pneumonia in older patient, eventually resulting into sever pneumonia. Pneumonia has been estimated to occur in about one third of patients with stroke. The most important factor contributing to the risk of pneumonia in patients with stroke is suggested to be dysphagia with aspiration. Angiotensin-converting enzyme inhibitors（ACEIs）have been reported to prevent pneumonia in elderly patients with stroke and improve silent aspiration. On the contrary, it was previously reported that a traditional Chinese herbal medicine, Banxia Houpu Tang（BHT, Hange Koboku-To in Japanese, formula magnolia et pinelliae）, improved swallowing reflex in patients with stroke and Parkinson's disease and improved cough reflex in patients with stroke. Furthermore, an intensive oral care which is represented by teeth and gingiva cleaned by caregivers is demonstrated to be able to reduce the incidence of pneumonia by improving cough reflex sensitivity. The author had taken a charge of a large number of patients with the dementia because of cerebrovascular disease（CVD）, Parkinson's Disease（PD）and Alzheimer's disease（AD）and experienced a large number of aspiration pneumonia and many related mortality. To those patients, antibiotic therapy was done, however the clinical result was not necessary satisfactory. So it was thought to be important and desirable to prevent the patients with aspiration pneumonia complicated with neurological diseases. In this article, whether treatment by BHT with simultaneous administration of ACEI in addition to intensive oral care can prevent aspiration pneumonia and reduce pneumonia-related mortality in 11 participants（male: female=6:5）who had experienced aspiration pneumonia as a past history. To those patients who had past histories of aspiration pneumonia previously, BHT with ACEI was administered for 24 month and oral care was strictly underwent. Only 1 patient of the present 11 elderly patients（1/11: 9.1 %）developed pneumonia and was transferred to the hospital, receiving antibacterial treatment during admission, however there were no patients with death with complete remission. Fortunately, no adverse events were observed in this combination therapy. The incidence of aspiration pneumonia or silent pneumonia were surprisingly decreased by this treatment and oral care management. From these facts, it was strongly suspected that simultaneous administration of BHT with ACEI had a beneficial action to prevent aspiration pneumonia which is suspected to be by a function of elevating serum or salivary substance P. It was strongly suggested that these treatments could decrease significantly the rate of pneumonia and a tendency of pneumonia-related mortality of the elderly patients with cerebrovascular diseases. During the observed 24 months, vital signs, blood cell counts and liver and renal function of the elder patients were within normal limits and adverse effect of these two drugs were not recog-

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nized.

In conclusion, it is possibly speculated that treatment with BHT with ACEI in addition to oral care can reduce the risk of aspiration or silent pneumonia in elderly patients with dementia.

Key words: Aspiration pneumonia, Banxia Houpu Tang, dementia, Angiotensin converting enzyme inhibitor (ACEI), Oral care

INTRODUCTION

Pneumonia is a major cause of mortality and morbidity, particularly among those who are older and debilitated. Pneumonia is not only a common infection in elderly people, but is also the most common cause of death in this population [1]. Marked depression of swallowing and cough reflexes is observed in patients with aspiration pneumonia [2]. And the increased incidence of pneumonia and the high mortality are consequences of aged-related factors, including coexisting illness, therapeutic interventions, and the aging process [1]. Pneumonia has been estimated to occur in about one third of patients with stroke [4]. The most important factor contributing to the risk of pneumonia in patients with stroke is suggested to be dyspahagia with aspiration [1]. ACEI has been reported to prevent pneumonia in elderly patients [5]. And ACEI has been shown to improve silent aspiration [6], and prevent pneumonia in elderly patients with stroke[7]. However, little is known about whether ACEI has a beneficial role in reducing the risk of pneumonia as compared to other classes of antihypertensive drugs in elderly patients with stroke. Meanwhile, in a number of observational studies conducted among older Japanese populations, the use of ACEI, but not other blood pressure-lowering drugs, has been associated with a reduced risk of pneumonia. Among populations who were older and debilitated, in whom silent aspiration of oropharyngeal pathogens is believed to be a leading cause of pneumonia, it is possible that established effects of ACEI on cough and swallowing may provide protection against infection. The effect of ACEI on swallowing and cough reflexes is strongly suspected to help prevent pneumonia [5, 6]. On the contrary, it was previously reported that BHT improved swallowing reflex in patients with stroke and Parkinson's disease [8, 9] and improved cough reflex in patients with stroke and Parkinson's disease and improved cough reflex in patients with stroke [10-12].

By the way, Watanabe et al reported that an intensive management of oral cavity which was represented by teeth and gingiva cleaned by caregivers at nursing homes could reduce the incidence of pneumonia by improving cough reflex sensitivity [13]. Therefore, whether treatment by BHT with simultaneous ACEI administration in addition to intensive oral care can reduce the risk of pneumonia in patients with dementia on account of neurological diseases was investigated in the present study.

The author experienced eleven patients who had suffered from aspiration pneumonia between January, 2009 and December, 2010 at the long-term care facility for handicapped elderly people located at Kisukicho, Unnan city (called as Nursing homes (NH): SAKURA-EN). Therefore, in the present study, BHT with simultaneous ACEI were administered to the 11 patients who had past histories of aspiration pneumonia with admission at nearby hospital and examined whether these two drugs had the inhibitory function of refractory aspiration pneumonia or preventing function of aspiration pneumonia in the elderly patients with dementia. Furthermore, it was also examined whether administration of BHT with simultaneous ACEI reduced the risk of pneumonia in patients with dementia with neurological diseases.

PATIENTS AND METHOD

The 11 patients with dementia recruited (6 men and 5 women; mean age±standard deviation (84.8±6.1 years old) were those who had been diagnosed additionally with either CVD, PD or AD as the specific cause of the dementia, or various combinations of these three conditions. Patients were recruited from the long-term care facility for handicapped elderly people located at Kisukicho, Unnnan city (called as Nursing homes (NH): SAKURA-EN) (Table 1). Diagnoses of CVD, AD, and PD were made according to the International Classification of Diseases, Tenth Revision (ICD-10). Before the treatment, exclusion criteria have been defined as follows. Briefly, none

of the patients had brain stem infarcts, sever liver disease (liver cirrhosis or chronic viral hepatitis), or renal dysfunction (serum creatinine >2.0 mg/dL). There were no patients who had a serious brain disease other than AD or PD, chronic lung disease and malignant disease. The use of medications for coexisting medical conditions was not discontinued, but a change in regimen or a prescription of new drugs known to affect swallowing and cough reflexes such as amantadine was not permitted during the therapy. At the beginning of the treatment, the purpose of the administration of those two drugs was explained to each families and informed consent was obtained before the start of the treatment. Furthermore, adequate care was taken to protect the privacy of the individuals participating in the study. All patients never discontinued during treatment during 24 months from the start of this treatment. The present participated patients' profile about disease, age, duration of illness is shown at Table 1.

Table 1. Patients were recruited from the long-term care facility for handicapped elderly people located at kisukicho, unnnan city (called as Nursing homes (NH): SAKURAEN). They were suffered from aspiration pneumonia at least more than one time. The present participated patients' profile about disease, age, duration of illness.

Patients profiles ***From January 2010 to December 2011***

11patients suffered from aspiration pneumonia at nursing home (SAKURAEN)

Age: mean±SD 84.8±6.1years Sex male:female 6:5

	Duration of illness
◆Cerebrovascular disease (CVD):5 cases	**11.6 years**
◆Parkinson's disease (PD): 3cases	**9.6 years**
◆Alzheimer's disease (AD): 2cases	**8.6 years**
◆CVD+PD: 1case	**7.6 years**

1 patient was transferred to the associated hospital because of aspiration pneumonia during follow-up 2years

Complicated diseases:1)Hypertention 11cases 2)Diabetes Mellitus 4cases

3)Hypercholesteremia 5cases 4)Renal dysfiunction 3cases 5) Liver dysfunction 2cases
6)Ischemic heart disease 2case 7)Chronic heart failure 1 case 8)Respiratory dysfunction 2cases

Enrolled patients in the present study

7 patients *From January 2010 to December 2011*

7 patients which suffered from aspiration pneumonia at nursing home (SAKURAEN) at least more than one time *(From January 2010 to December 2011)*

Disease	*Patient number*	*Sex*	*Duration of illness*
◆ CVD	3 patients	(M:F 2:1)	11.6 years
◆ PD	2 patients	(M:F 0:2)	9.8 years
◆ CVD+PD	1 patient	(M:F 1:0)	8.6 years
◆ CVD+AD	1 patient	(M:F 0:1)	7.6 years

total M:F 3:4

Foods feeding methods : **6 patients took foods orally**
: **1 patients took foods via PEG tube**

 # Cerebrovascular disease (CVD) Parkinson's disease (PD) Alzheimer's disease (AD)

BHT obtained from Tsumura Co., Ltd. (Tokyo, Japan) was used to the present patients. Patients with body weight of 50 kg or more took 2.5 g of the powder wrapped in white paper orally before each meal, three times a day and patients with body weight less than 50 kg took 2.5 g of the powder twice a day (5.0 g powder/day). And simultaneously low dose of ACEIs (enalapril maleate 2.5mg~5.0mg/day or imidapril hydrochroride 2.5mg~5.0 mg/day) were administered to those patients (Fig. 1). The dosages of ACEI was regulated without affecting the blood pressure during follow up-24monts period. If the blood pressure was under normal pressure level, ACEI administration was scheduled to stop immediately. The present 11 patients received angiotensine recerptor blocker (ARB) (6/11: 54.5%), calcium antagonist (4/11: 36.4%), diuretics and/or α/β blocker (1/11: 9.1%) as antihypertensive drugs for the control of daily blood pressure. Fortunately, there were no patients with discontinuation of ACEI because of lowering blood pressure and other circulatory events. Before this combination therapy, 11 patients received uniform evaluations including medical histories, laboratory tests (blood count and routine chemistry, including liver and renal functions), neurological examinations as well as assessments of activities of daily living (ADL). The primary outcome measures were defined as the number of patients who developed pneumonia and the number of patients who died from pneumonia. Chest x-ray was performed when body temperature was higher than 37.5°C for more than 48 hours or whenever Chest X-ray was judged necessary. Pulmonary chemical injury according to witnessed aspiration was diagnosed as aspiration pneumonia [11]. Pneumonia was defined fatal if the individual died within 28 days of the diagnosis [12]. Febrile days during which a patient's body temperature was higher than 37.5°C and days during which a patient was treated with antibiotics for any reason were also recorded. Influenza vaccination was done to all patients. Because adverse effects of BHT were examined, vital signs and the amount of orally self-ingested calories were recorded daily and examined monthly as assessments. Laboratory tests (blood cell counts and routine chemistry, including liver and renal functions) were assessed at 6, 12 and 24 month from the beginning of the study. ADL of each patient was reassessed at the end of the

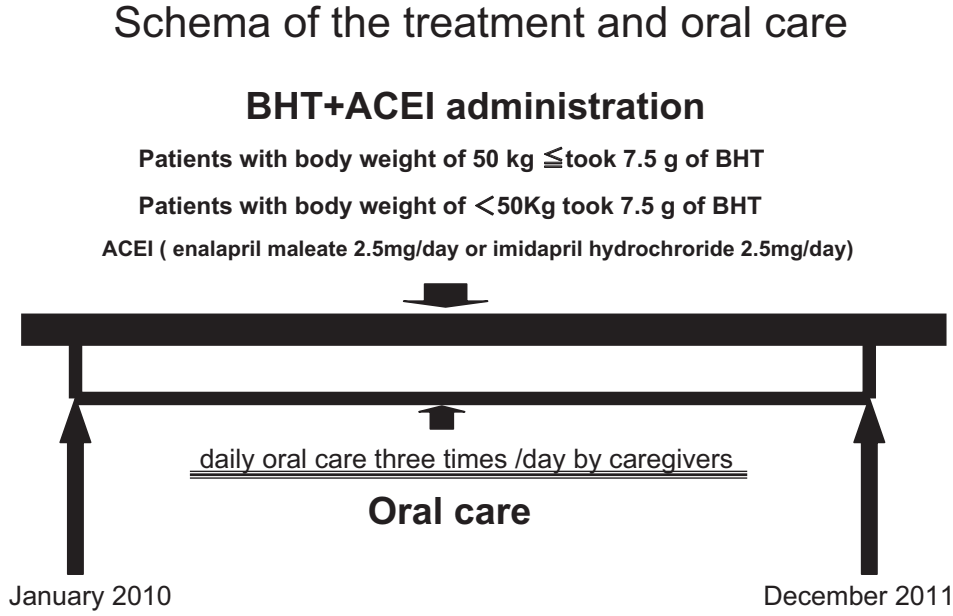

Fig. 1. Schedule of this study. Patients with body weight of 50 kg or more took 2.5 g of BHT orally before each meal, three times a day and patients with body weight less than 50 kg took 2.5 g twice a day. And simultaneously low dose of ACEIs (enalapril maleate 2.5mg~5.0mg /day or imidapril hydrochroride 2.5mg~5.0 mg/day) were administered to those patients.
Furthermore, oral care management was underwent to prevent oral bacterial infection.

observation period. All these data were recorded on a card prepared for each case.

RESULTS

Among the 11 patients of the present study, some patients took foods orally by caregivers and two patients took food by percutaneous endoscopic gastric (PEG) tube. No patients took cholinesterase inhibitors, and some of the patients took antipsychotics and dopamine agonists. All 11 patients were administered BHT with ACEI orally or via PEG tube during follow-up periods and received daily oral care three times / day for 24 months. Among the present 11 patients during the 24 months follow up periods, only 1 patient developed aspiration pneumonia and moved to associated facility of another hospital. This patient was a 92 year old woman with PD. Before administration of those drugs, she was suffered from aspiration pneumonia at least twice per a year and she was transferred to the nearby hospital. She was immediately treated by administration of antibacterial drug and intravenous infusion of Linger's solution approximately for 3weeks admission (Fig. 2). But, this patient had not been suffered from pneumonia at all since treatment by BHT with ACEI and oral care by caregivers were started. This treatment was extremely effective for this patient. Then, there was not another occurrence of pneumonia and pneumonia-related death during the observation period. However, 2 patients suffered from ischemic heart disease and 1 patient suffered from bronchial asthma during observation time. But these diseases did not influence their lives at all. The incidence of aspiration pneumonia or silent pneumonia surprisingly decreased by administration of BHT with ACEI and daily oral care management and the incidence of pneumonia and pneumonia-related mortality decreased significantly by these treatments. In general, oral cavity dryness increases because of decreased salivary discharge volume in the elderly populations. So it is easily suspected that such a worst oral circumstance is a source of breeding of bacterial contamination. Finally breeding of some kinds of bacteria is thought to invade into the main trachea, eventually their distal branches and cause silent or aspiration pneumonia

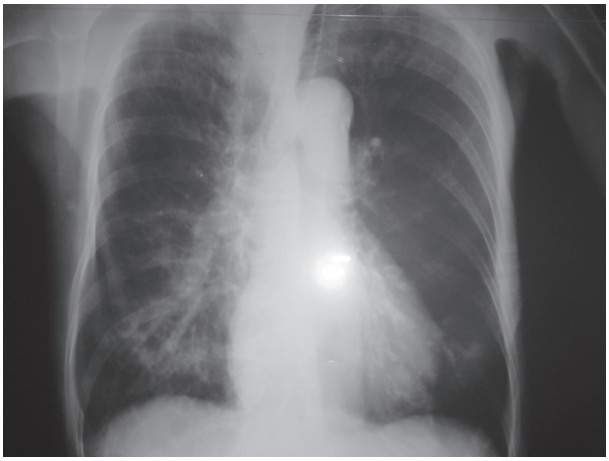

Fig. 2. Among the present 11 patients, only 1 patient developed aspiration pneumonia and moved to associated facility of another hospital. This patient was a 92 year old woman with PD. She was suffered from aspiration pneumonia at least 2times per a year and she was transferred to the nearby hospital. The chest X ray demonstrated a pneumonia shadow at right lower field.

in the elderly patients. In the present study, what kind of bacteria was cultured in the oral cavity was examined in the 11 patients. The result showed that *Streptococcus pneumonia* in 8 patients, *Moraxella catarrhaslis* in 2 patients and *Klebsiella pneumonia* in 1 patient were cultivated by their suptums. During the observed 24 months, vital signs, blood cell counts and liver and renal function of the elder patients at the nursing home were within normal limits and there was not a patient with malnutrition. Furthermore, it was prominently important that adverse effects of BHT and ACEI were not recognized at all during 24 months (Table 2)

DISCUSSION

Pneumonia is the most common cause of death in the elderly. The increased incidences of pneumonia and high mortality are consequence of a number of aged-related factors, including coexisting illnesses, therapeutic interventions, and the aging process itself [13]. Pneumonia has been estimated to occur in about one third of patients with stroke [1, 3, 13]. The most important factor contributing to the risk of pneumonia of patients with stroke is suggested to be dysphagia [1, 16]. ACEI has been shown to decrease a silent aspiration and prevent pneumonia in elderly patients with stroke [14, 15]. It was demonstrated that ACEI could reduce the

Table 2. During the observed 24 months, vital signs, blood cell counts and liver and renal function of the elder patients at the nursing home were within normal limits and there was not a patient with malnutrition. Furthermore, severe adverse effects by administration both of BHT and ACEI were not recognized during 24 months.

Changes of laboratory data, life style, adverse effect of drug

	baseline	12 months	24 months
★vital sign	stable	stable	stable
★RBC	334±28.6 x 10^4/mm^3	331±38.5 x 10^4/mm^3	364±48.6 x 10^4/mm^3
★WBC	5,600±820.6/ mm^3	5,500±758.9/mm^3	5400±758.9/mm^3
★PLT	17.4±2.5/mm^3	16.4±2.1/mm^3	18.4±2.7/mm^3
★liver function			
ALT	12.4±2.1 IU /l	13.4±1.7 IU /l	13.4±1.1 IU/l
AST	22.4±1.8 IU /l	17.4±2.1 IU /l	22.4±211 IU /l
T-Bil	0.9±0.08mg/dl	0.8±0.04mg/dl	1.1±0.06mg/dl
★renal function			
BUN	24.9±1.7mg/dl	23.6±1.9mg/dl	25.9±2.8mg/dl
Crea	1.22±0.08mg/dl	1.33±0.05mg/dl	1.25±0.07mg/dl
★ADL	normal	normal	normal
★total amount of orally self-ingested calories	1345.8±125.5Kcal	1405.8±165.8Kcal	1398.8±129.5Kcal
★adverse effect of BHT	none	none	none
★adverse effect of ACEI	none	none	none

risk of pneumonia as compared to other antihypertensive drugs such as calcium channel antagonists or diuretics. The present study demonstrated that BHT with simultaneous administration of ACEI treatment reduced the risk of pneumonia and tended to reduce the rate of pneumonia-related mortality. And ADLs were maintained without major adverse events. It was reported that treatment by ACEI was effective in preventing onset of pneumonia and related mortality in association with increase of serum substance P level [3]. Furthermore, amantadine and oral care have been reported to prevent aspiration pneumonia [17, 18], but pneumonia is still a major cause of death in disabled elderly people. Meanwhile, it was previously reported that BHT improved swallowing reflex in patients with stroke and Parkinson's disease [8, 9] and improved cough reflex in patients with stroke [8-11]. BHT is a one of the most basic recipes in traditional Chinese medicine; it was established 1,800 years age and has been widely used for the treatment of depression in many countries in East Asia [10, 11]. In Japan, it is made of pharmaceutical-grade herbs that are quality controlled by the Japanese Pharmacopoeia. According to this surveillance system, many kinds of adverse effects of herbs have been reported, such as hypopotassemia from licorice root [19] and interstitial pneumonia from skullcap [20]. But since 1975, the year BHT first became available as a medical drug under the Japanese government medical insurance system, no severe adverse events have been reported and the official price of BHT in Japan is low which is economically reasonable for the prevention of aspiration pneumonia in high-risk elderly people.

Silent aspiration, which frequently occurs in patients with basal ganglia infarctions, may be an important risk factor for pneumonia in elderly people [20]. Impairments of swallowing and cough reflexes, which are related to substance P, increase the risk of aspiration pneumonia [21]. BHT has been reported to improve these reflexes in patients with stroke and PD, probably due to an increase in substance P levels in saliva [6-8]. In animal models, polysaccharides contained in BHT increase dopamine and 5-hydroxytryptamine levels in the whole brain and decrease dopamine turnover in the hippocampus of mice [14]. These mechanisms may

be responsible for the beneficial effects of BHT on swallowing and cough reflexes. In the present study, among 11 elderly patients with aspiration pneumonia as a past history, only 1 patient suffered from pneumonia. However the rest 10 patient did not suffer from aspiration pneumonia. Accordingly, mortality related to pneumonia decreased by administration of BHT with simultaneous administration of ACEI. It was strongly speculated that some mechanism of inhibiting dysphagia by combined treatment with BHT accompanied with ACEI reduced the rate of pneumonia and affect related mortality rate. Consequently, it was showed that combined therapy might be directly responsible for lower incidence of pneumonia and mortality from pneumonia in the elderly patients with dementia. Pulmonary chemical injury associated with witnessed aspiration is defined as aspiration pneumonitis, whereas aspiration pneumonia is an infectious process in the lower respiratory tract that requires antibiotics for treatment [15]. Because there is some overlap between these syndromes, it is sometimes difficult to differentiate them accurately. In this study, pulmonary chemical injury according to witnessed aspiration was diagnosed as pneumonitis and was excluded from aspiration pneumonia, although it was necessary to distinguish pneumonitis with unwitnessed aspiration from pneumonia. The means by which BHT affect the respiratory system are thought to be through elevation of serum substance P, a neurotransmitter for primary sensory afferent nerves. It has been pointed that elevated levels of serum substance P are associated with cough and may also produce the enhanced swallowing reflex [3, 21]. The same mechanism of inhibiting the rate of dysphagia has been pointed in the elderly patients under the treatment by administration of ACEI [11, 14]. However, if high dose of ACEI is administered to prevent pneumonia in the elderly patients, it is worried about the adverse effect by original ACEI adverse effect such as cough and lowering blood pressure. So if inhibiting dysphagia is designed to achieve, high dose of ACEI should not be administered to the elderly patients with dementia to prevent aspiration pneumonia. Accordingly, BHP plus low dose of ACEI must be used to hope the increasing the power of the two drugs in comparison to monotherapy of BHT or ACEI. By administration of these two drugs, an increased cough reflex and improved swallowing provide a reasonable basis for a decreased risk of aspiration pneumonia. Furthermore, Watanabe et al demonstrated that an intensive management of oral cavity which was represented by teeth and gingiva cleaned by caregivers at nursing homes could reduce the incidence of pneumonia by improving cough reflex sensitivity. In the present 11 patients, daily oral care was conducted by caregivers. And it was strongly suspected that total oral bacterial numbers were decreased by daily cleaning oral cavity. In the recent days, elderly people is increasing and it is easily in expectation of increasing patients with advanced dementia such represented by CVD, PD and AD. Nursing homes (NHs) play an important role in their end of life care. Infections, particularly pneumonia, are common in individuals with advanced dementia [20]. Nursing home residents with end stage dementia who develop pneumonia are often treated with antimicrobial agents, and many are hospitalized. However, the benefits of antimicrobial treatment are not well established in this population, and there is a substantial variation in practice [22]. Current literature provides limited and contrasting information on the ability of antimicrobial agents to affect 2 important treatment goals in advanced dementia: survival and comfort. Antimicrobial treatment of suspected pneumonia episodes is associated with prolonged survival but not with improved comfort in nursing home residents with advanced dementia [23]. In the present study, it was demonstrated that BHT with simultaneous administration of ACEI improved swallowing reflex in patients with stroke and Parkinson's disease and improved cough reflex in patients with stroke. Therefore, we must consider that this treatment in sever staged patients with dementia by stroke and Parkinson's disease reduces risk of pneumonia, especially in the point of preventing aspiration pneumonia. In conclusion, the present report suggested that treatment by BHT with ACEI had a high possibility of preventing the onset of aspiration pneumonia of the elderly patients with dementia and/or stroke without sever adverse effects.

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