Original Article

Expression pattern of soluble triggering receptor expressed on myeloid cells-1 in mice with *Acinetobacter baumannii* colonization and infection in the lung

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Background: *Acinetobacter baumannii* (*A. baumannii*) is one of the most troublesome opportunistic pathogens associated with hospital-acquired pneumonia (HAP). It is important to be able to discriminate *A. baumannii* colonization from infection in its early stages so that effective antibiotics can be promptly applied. Recent studies have reported that the secretion of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) is markedly upregulated in pneumonia and sepsis, but the expression pattern of sTREM-1 in *A. baumannii* colonization and infection in the lung has not been explored.

Methods: C57BL/6J male mice were intraperitoneally injected with 1% streptozotocin for 5 consecutive days to establish diabetic models. Subsequently, aerosol inhalation of *A. baumannii* suspension was performed in these mice to induce pulmonary colonization or infection with saline as vehicle control. Mice were sacrificed and lung tissue was harvested on days 0, 1, 3, 5 and 7 after exposure. Pharyngeal swab culture, lung homogenate culture, and H&E staining of lung tissue were performed to assess the severity of infectious inflammation. sTREM-1 expressions in serum and lung supernatants, serum procalcitonin (PCT) and C-reactive protein (CRP) concentrations were measured by ELISA.

Results: *A. baumannii* colonization and infection models were verified by pharyngeal swab culture, lung homogenate culture, and H&E staining. While sTREM-1 concentrations in mice with *A. baumannii* colonization remained unchanged in serum and lung supernatants, sTREM-1 expression levels in infected animals were significantly upregulated. In addition, serum sTREM-1 concentration was positively correlated with serum levels of PCT and CRP.

Conclusions: Dynamic secretion of sTREM-1 is associated with the development of *A. baumannii* infection in the lung. Therefore, sTREM-1 expression level may be a promising biomarker for discriminating *A. baumannii* infection from colonization.

Keywords: Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1); *Acinetobacter baumannii*; pulmonary infection; colonization; procalcitonin (PCT)

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Introduction

Acinetobacter baumannii (*A. baumannii*) is a pleomorphic aerobic gram-negative bacillus exclusively isolated from the hospital and hospitalized people. *A. baumannii* has low virulence and motility, but it is capable of causing pulmonary infections in vulnerable people with compromised immune function. Currently *A. baumannii* has emerged as one of the most common and troublesome opportunistic bacterial pathogens in hospital-acquired pneumonia (HAP) (1,2). The carriage ratio of *A. baumannii* in patients from an intensive care unit is approximately 75%. Even in healthy humans with normal immune systems, its carriage ratio is as high as 25% (3). Due to its multi-drug resistance, there is no clearly effective therapy for HAP caused by *A. baumannii* (4), which therefore results in results in a mortality rate of 52% (1).

Bacterial colonization, defined as the presence of bacteria on the body surface including the airway without causing clinical evidence of infection in the individual, is the prerequisite of *A. baumannii* infection (5). *A. baumannii* colonization does not necessarily lead to pulmonary infection, but it does increase the risk of infection (6). It is difficult to tell whether *A. baumannii* observed in the culture of respiratory tract samples is infection or colonization (7), especially in patients with multiple co-morbidities, concurrent infections, and who are on prolonged courses of antibiotics. Procalcitonin (PCT) and C-reactive protein (CRP) are commonly used serum biomarkers for diagnosing infections. CRP has relatively low specificity and serum CRP level can be increased in a number of other conditions including trauma, tumor, and autoimmune diseases (8). Compared with CRP, serum PCT concentration has a better diagnostic value due to its high specificity and early response to bacterial infection (9). However, reliable serum biomarkers for distinguishing between *A. baumannii* infection and colonization have been barely reported so far.

Triggering receptor expressed on myeloid cells-1 (TREM-1) is an immunoglobulin expressed on the surface of myeloid cells that was discovered by Bouchon *et al.* in 2000 (10). Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) is the soluble form of TREM-1. Increasing numbers of studies have reported that sTREM-1 is secreted into the blood and other body fluids when bacterial infections occur and sTREM-1 levels are closely correlated with the severity of infection (11,12). However, whether sTREM-1 expression levels are different between *A. baumannii* infection and colonization in the lung has been unknown so far.

In this study, we established a murine model of *A. baumannii* colonization and infection, and investigated the expression pattern of sTREM-1 in mice with *A. baumannii* infection or colonization. The correlation between serum sTREM-1 and PCT or CRP concentrations were further analyzed.

Methods

Reagents

Streptozotocin and sodium citrate buffer were purchased from Sigma (St. Louis, MO, USA). Mouse/Rat TREM-1 Quantikine ELISA Kit and Mouse C-Reactive Protein/CRP Quantikine ELISA Kit were obtained from R&D Systems (Minneapolis, MN, USA). Mouse PCT ELISA kit was obtained from USCN (Wuhan, Hubei, China).

Animals

This study was approved by the Institutional Review Board of Central South University and carried out in strict accordance with the guidelines approved by the Animal Care and Use Committee of Central South University. Specific-pathogen-free C57BL/6J male mice (4–6 weeks of age) were purchased from the Center of Laboratory Animals, Central South University (Changsha, Hunan, China). Animals were housed in a specific-pathogen-free laminar-flow atmosphere under controlled temperature, humidity and light with a standard rodent chow diet. Animal experiments were performed after the mice had been acclimated for 1 week.

Experimental design

Mice were randomly divided into a diabetic group (n=150) and a non-diabetic group (n=20). Mice in the diabetic group were injected with 1% streptozotocin (70 mg per kg of body weight) intraperitoneally for 5 days (once per day), while mice in the non-diabetic group were injected with the same volume of sodium citrate buffer (0.1 M, pH =4.5). Tail vein blood glucose was measured in all mice after 10 days, and mice with random blood glucose higher than 16.7 mM were considered to be diabetic. Subsequently, diabetic mice were randomly divided into control, colonization, and infection groups (n=50). Using an ultrasonic atomizer (Rochester, NY, USA), mice

Table 1 The body weight changes (g) of mice after modeling

Time point	Non-diabetic	Control	Colonization	Infection
Day 1	0.35±0.19	−0.95±0.17	−0.88±0.17	−1.37±0.37*#
Day 3	0.56±0.25	−0.23±0.17	−0.34±0.12	−1.39±0.51*#
Day 5	0.43±0.28	−0.26±0.08	−0.41±0.16	−1.65±0.33*#
Day 7	0.98±0.12	−0.34±0.06	−0.32±0.12	−1.39±0.52*#

*, P<0.05 compared with the control group at the same time point; #, P<0.05 compared with the colonization group at the same time point.

in the colonization and infection groups inhaled a suspension solution of *A. baumannii* at concentrations of 1×10^9 CFU/mL and 1×10^{11} CFU/mL, respectively, for 1 h while mice in the control group inhaled saline. Inhalation doses of *A. baumannii* were chosen based on previous studies (13,14). These mice were euthanized and sacrificed on Days 0, 1, 3, 5 and 7 (n=10 at each time point, mice on Day 0 were sacrificed immediately after *A. baumannii* inhalation). Blood and pharyngeal swab samples were collected directly after euthanasia. Blood was centrifuged at 3,000 rpm for 5 min to obtain serum samples. For 5 mice in each group, the right lung of each animal was dissected for homogenate culture and the left lung for H&E staining. For the other 5 mice in each group, whole lung homogenate was performed as previously described (15). Briefly, whole lung tissue from each animal was prepared by homogenization in PBS-containing protease inhibitors (Complete, Roche Diagnostics). Lung homogenate was subsequently centrifuged at 12,000 rpm for 10 min at 4 ℃, and the supernatant was collected.

H&E staining

Tissue from the left lung was submerged and fixed in 4% paraformaldehyde at 4 ℃ for 24–48 hours and embedded in paraffin. Sections (4 μm) were stained with hematoxylin and eosin, and the morphological changes of the lungs were observed under a light microscope (Leica Microsystems, Wetzlar, Germany).

Pharyngeal swab and lung homogenate culture

Pharyngeal swabs were collected by gently swabbing the palatine arches and pharynx of each mouse and dissolved in pathogen-free saline. Tissue from the right lung was weighed, minced, immersed in pathogen-free saline, and homogenized at 5,000 rpm for 20 min. After centrifugation at 3,000 rpm for 3 min, the supernatant was collected and diluted 10, 100, 1,000 and 10,000 fold with saline. 100 μL of each sample was evenly added onto blood agar plates (3 plates for each sample). Agar plates were inverted and put into a constant temperature incubator (37 ℃) for 24 h. *A. baumannii* colonies were confirmed by the Department of Clinical Laboratory, Xiangya Hospital (Changsha, Hunan, China). The number of colonies for each sample was subsequently counted and the logarithmic value of bacteria number per gram of lung tissue weight from each mouse was calculated.

Measurement of serum sTREM-1, PCT and CRP

sTREM-1, PCT and CRP concentrations in serum and lung supernatants were determined using commercially available ELISA kits according to the manufacturer's instructions.

Statistical analysis

Data were analyzed with the Statistical Package for the Social Sciences version 13.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation (SD), and comparisons between groups were evaluated using an independent *t*-test. Pearson correlation analysis was performed to evaluate the correlation between serum sTREM-1 and PCT or CRP concentrations in mice with *A. baumannii* inhalation. A P value <0.05 was considered to be statistically significant.

Results

Presentation of A. baumanni infection in mice

After *A. baumannii* inhalation, the mice in the infection group appeared to have decreased food intake and physical activity and body weight loss (*Table 1*). Some mice in the infection group displayed signs of conjunctivitis. In

Table 2 *A. baumannii* colony counting (lg CFU/g) in lung homogenates

Time point	Colonization	Infection
Day 0	3.04±0.26	6.45±0.67#
Day 1	2.95±0.22	8.41±0.34#
Day 3	2.67±0.15	9.76±0.47#
Day 5	2.62±0.25	10.02±0.28#
Day 7	2.56±0.14	10.03±0.21#

The colony numbers are converted into common logarithms to facilitate graphic presentation; #, P<0.05 compared with the colonization group at the same time point.

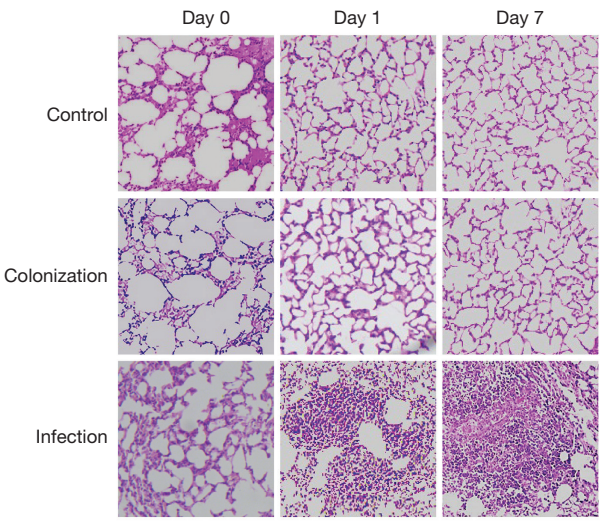

Figure 1 Histology changes in lung tissue of mice from non-diabetic, control, colonization and infection groups at different time points after modeling by H&E staining (×200). Mild pulmonary edema was seen in the control and colonization groups on Day 0, which disappeared the next day, while lung tissue of the mice in infection group showed significant inflammatory cells infiltration, destruction of alveolar structure and exudation in alveoli.

contrast, mice in the non-diabetic, control, and colonization groups were overall healthy and did not present any of these symptoms.

Confirmation of A. baumannii colonization and infection

A. baumannii colonies grew from pharyngeal swab and lung homogenate samples from both the colonization and infection groups, while no colonies were observed in the non-diabetic and control groups. In the colonization group, the colony number of lung homogenate samples was maximal on Day 0 and gradually decreased on subsequent days. However, the colony numbers in the infection group displayed a rapid increase during the first 3 days, peaked on Day 5, and maintained at a stable level for the last 2 days (*Table 2*).

Consistently, histology examination showed that only mild pulmonary edema was seen in lung tissue from control and colonization group mice on Day 0, evidence of which was no longer apparent on the following day. In contrast, lung tissue from infection group mice presented with inflammatory cell infiltration, destruction of alveolar structure, and exudation in the alveoli (*Figure 1*). Taken together, these data confirmed that the murine model of *A. baumannii* colonization and infection used in this study was successful.

sTREM-1 levels in serum and lung supernatants were elevated after A. baumannii infection but not colonization in the lung

As shown in *Figure 2*, consistent with *A. baumannii* colony counts, sTREM-1 concentration also showed a quick and substantial elevation from Day 1 to Day 5, and remained overall stable during the next 2 days, suggesting that the production of sTREM-1 was correlated with development of *A. baumannii* infection in lung. There was no statistically significant difference in sTREM-1 levels in serum or lung supernatants among non-diabetic, control, and colonization groups. Interestingly, in the infection group, sTREM-1 concentrations in serum and lung supernatants were significantly elevated, approximately to 2-fold compared with control or colonization groups (*Figure 2*).

Serum levels of sTREM-1 were positively correlated with PCT and CRP

To further assess the diagnostic value of serum sTREM-1 in *A. baumannii* infection, we investigated the correlation between serum levels of sTREM-1 and PCT or CRP. A significant increase of PCT and CRP in serum was observed after *A. baumannii* infection (*Figures 3,4*). There was no significant difference in PCT concentrations among non-diabetic, control, and colonization groups. However, compared with the non-diabetic group, CRP concentrations were significantly higher in control and colonization

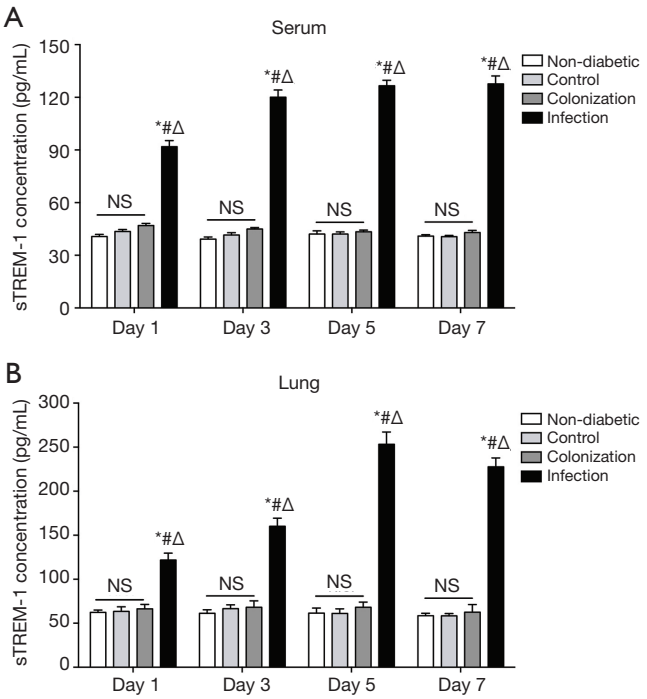

Figure 2 sTREM-1 concentrations in serum (A) and whole lung supernatants (B) of mice from non-diabetic, control, colonization and infection groups at different time points after modeling. *, P<0.05 compared with non-diabetic group; #, P<0.05 compared with control group; Δ, P<0.05 compared with colonization group at the same time point. sTREM-1, soluble triggering receptor expressed on myeloid cells-1; NS, not significant

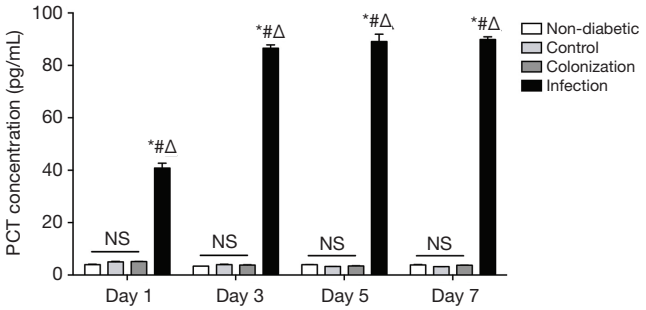

Figure 3 Serum PCT concentrations of mice from non-diabetic, control, colonization and infection groups at different time points after modeling. *, P<0.05 compared with non-diabetic group; #, P<0.05 compared with control group; Δ, P<0.05 compared with colonization group at the same time point. PCT, procalcitonin; NS., not significant.

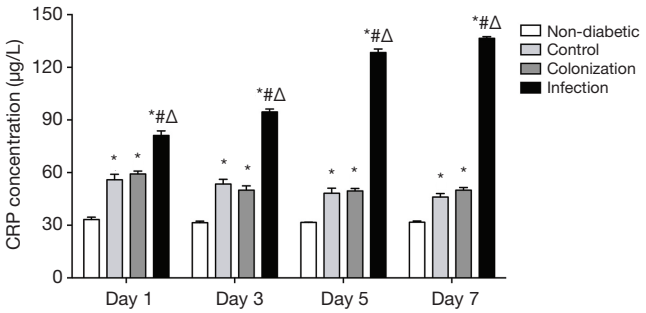

Figure 4 Serum CRP concentrations of mice from non-diabetic, control, colonization and infection groups at different time points after modeling. *, P<0.05 compared with non-diabetic group; #, P<0.05 compared with control group; Δ, P<0.05 compared with colonization group at the same time point. CRP, C-reactive protein.

groups, but no difference was seen between control and colonization groups.

Importantly, Pearson correlation analysis revealed that the elevated serum level of sTREM-1 during the infection time course was positively correlated with PCT (r=0.983, P<0.001) and CRP (r=0.866, P<0.001) (*Figure 5*), suggesting that like PCT and CRP, sTREM-1 may be used as a serum biomarker for *A. baumannii* infection.

Discussion

A. baumannii is the most common pathogen that colonizes the body surfaces of patients and health care workers. In the last decade, *A. baumannii* has become one of the main opportunistic pathogens in HAP. Early and accurate diagnosis of *A. baumannii* infection in the lung is of fundamental importance for effective therapies. In the present study, we found that the serum level of sTREM-1 was markedly elevated after *A. baumannii* infection but not colonization in a diabetic murine model. Furthermore, the changes of sTREM-1 concentration after infection positively correlated with serum levels of PCT and CRP.

Distinguishing infection from colonization remains a major challenge for the diagnosis of *A. baumannii*, especially when patients do not present clear or characteristic symptoms. A mistaken decision will either cause improper use of antibiotics and severe antibiotic resistance, or put patients in a risky situation because of delayed antibacterial treatment. Valuable biomarkers or techniques that could facilitate accurate diagnosis of *A. baumannii* infection are therefore urgently needed. The prerequisite for exploring

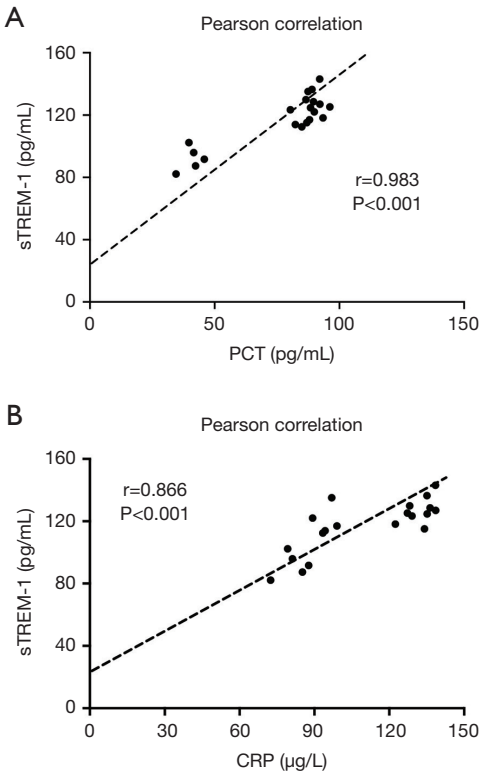

Figure 5 Pearson correlation analysis between the serum levels of sTREM-1 and PCT or CRP in mice infected with *A. baumannii*. (A) Pearson correlation coefficient between sTREM-1 and PCT; (B) Pearson correlation coefficient between sTREM-1 and CRP. sTREM-1, soluble triggering receptor expressed on myeloid cells-1; CRP, C-reactive protein; PCT, procalcitonin.

potential biomarkers is the establishment of the animal model of *A. baumannii* infection and colonization. *A. baumannii* has relatively weak invasiveness and is not capable of infecting animals with a normal immune system. Previously, cyclophosphamide has commonly been used to generate animals with compromised immunity (16). However, most neutrophils are killed in this animal model and lethal infection develops within a short time frame, which makes it difficult to observe the dynamic pathological changes after infection. It has been reported that patients with diabetes are at significantly increased risk for the acquisition of *A. baumannii* infection (17). Thus, we used a murine model with streptozotocin-induced diabetes for *A. baumannii* infection based on based on previous studies (14,18-20). *A. baumannii* colonization and infection were successfully induced by using different doses of inhaled bacteria. This inhalational model of *A. baumannii* in diabetic mice provides a simple and effective approach to study *A. baumannii* colonization and infection, thus offering an alternative to existing models for future studies. Mild pulmonary edema and infiltration of inflammatory cells was seen in mice from the control and colonization groups directly after aerosol inhalation and disappeared the next day, which we thought was caused by the non-infectious irritation during inhalation.

TREM-1 is a receptor that triggers an inflammatory cascade and is highly expressed in neutrophils and monocytes (21). It has been reported that activation of TREM-1 immediately induces rapid degranulation of neutrophilic granules and drives the release of pro-inflammatory factors, including MIP-1, MCP-1 and IL-8, thus playing an important regulatory role in inflammation (22). sTREM-1, the soluble form of TREM-1, has been demonstrated to be produced and secreted into body fluids including blood during microbial infections, and its expression level is closely associated with the severity of infection, including HAP caused by *A. baumannii* (11,23). It is worth noting that the specificity of sTREM-1 in bacterial infection still remains controversial. Bouchon *et al.* reported that sTREM-1 was not upregulated in samples from patients with non-infectious inflammatory conditions like psoriasis, ulcerative colitis, or immune-complex mediated vasculitis, indicating that this receptor is specifically involved in infection (24). However, increasing amount of studies has shown that serum sTREM-1 is also significantly elevated in noninfectious inflammatory diseases (25-27). Phua *et al.* observed a significant elevation of serum sTREM-1 levels in patients with COPD and asthma exacerbations compared with control objects, although this elevation was greater in patients with *A. baumannii* associated pneumonia (28). In the present study, an elevation of sTREM-1 levels in serum was observed after *A. baumannii* infection, trending similarly to the increase of bacterial colonies. More importantly, we found that similar to PCT, which has been reported to be a biomarker to differentiate *A. baumannii* infection from colonization (29), there was a significant difference in sTREM-1 levels in both serum and lung supernatants between the colonization and infection groups. The serum level of CRP increased in mice of both control and colonization groups, which may be associated with the inflammatory counterpart of diabetes. A positive correlation between sTREM-1 and PCT or CRP further supports that serum sTREM-1 may also be used as a biomarker in *A. baumannii* infection. However, whether the combined detection of sTREM-1, PCT, and CRP in serum

could promote the diagnostic accuracy of *A. baumannii*-associated pneumonia is still unexplored.

There are several limitations in the present study. Firstly, data in the present study is obtained exclusively by using murine models instead of humans, which limit the interpretation of potential diagnostic value of sTREM-1 in *A. baumannii* infection. Furthermore, whether the elevation of sTREM-1 levels is correlated with the severity of *A. baumannii* infection remains undetermined. Future studies investigating sTREM-1 kinetics in human subjects with *A. baumannii* associated pneumonia and sepsis are therefore required to address these limitations.

In conclusion, we demonstrated that serum levels of sTREM-1 were upregulated in *A. baumannii* infection while it remained unchanged at the colonization stage. Furthermore, in *A. baumannii*-infected mice, sTREM-1 concentrations in serum were positively correlated with PCT and CRP. Collectively, these findings indicate that sTREM-1 may be a promising biomarker for differential diagnosis of *A. baumannii* colonization and infection in the lung.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Institutional Review Board of Central South University and conducted in accordance with the guidelines approved by the ethics committee.

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