Original Article
Yonsei Med J 2025 May;66(5):295-301
https://doi.org/10.3349/ymj.2024.0190
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Risk Factors for Failure to Eradicate Infection after Single Arthroscopic Debridement in Septic Arthritis of a Native Knee Joint

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Purpose: To identify the risk factors and effect of empirical glycopeptide on the failure of single arthroscopic debridement for septic knee arthritis in a native knee joint.

Materials and Methods: Patients who underwent arthroscopic debridement for septic knee arthritis from March 2005 to December 2022 at one institution were included in this study. Demographic data, comorbidities, preoperative factors including history of previous surgery, history of injection, laboratory data including preoperative C-reactive protein (CRP) and white blood cell (WBC) count, isolated pathogens from synovial fluid culture, and Gachter stage were analyzed. Statistical analyses using univariate and logistic regression were performed.

Results: Out of 132 patients, 17 patients (12.9%) had more than one additional arthroscopic debridement. History of diabetes mellitus (DM) (p<0.001), previous injection (p=0.041), isolated *Staphylococcus aureus* in synovial fluid (p=0.010), and high Gachter stage (p=0.002) were identified as risk factors, whereas age, history of previous knee surgery at the affected knee, CRP level, preoperative WBC, and preoperative neutrophil count of synovial fluid had no significant relation. Logistic regression analysis showed significant increase of risk in patients with DM [odds ratio (OR) 12.002, 95% confidence interval (CI) 3.243–44.418, p<0.001], previous injection history (OR 4.812, 95% CI 1.367–16.939, p=0.017), and isolation of *Staphylococcus aureus* in synovial fluid (OR 4.804, 95% CI 1.282–18.001, p=0.031) as independent risk factors for failure of infection eradication after single arthroscopic debridement.

Conclusion: Comorbidity of DM, history of previous injection, isolated *Staphylococcus aureus* in synovial fluid, and high Gachter stage were associated with a higher risk of failure to eradicate infection with a single arthroscopic procedure. Empirical glycopeptide administration also showed no significant benefit in reducing the risk of additional surgical procedures for infection control, suggesting against the routine administration of glycopeptide.

Key Words: Arthritis, infectious, arthroscopy, debridement, risk factors, treatment failure

Received: July 10, 2024 **Revised:** September 6, 2024 **Accepted:** September 19, 2024 **Published online:** December 31, 2024
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•The authors have no potential conflicts of interest to disclose.

INTRODUCTION

Septic arthritis of the knee joint is an orthopedic emergency that can lead to impaired joint function and, further, mortality due to sepsis from uncontrolled infection. The incidence of septic arthritis has gradually increased over the past decade, possibly in association with an increase in invasive procedures on the knee.[1,2] Risk factors for septic arthritis include diabetes mellitus (DM), rheumatoid arthritis, recent joint surgery, hemodialysis, poor socioeconomic status, intravenous injection, and immunosuppression.[2-8] Treatment of septic arthritis focuses on reducing the infection burden through prompt administration of adequate antibiotics, joint irrigation, and debridement. Considering that a delay in administering antibiotics of up to 24 to 48 hours can cause joint destruction and lead to joint dysfunction, the administration of empirical IV antibiotics is crucial.[9,10] However, there is no single IV antibiotic considered as a gold standard due to the variety of pathogens and their drug susceptibilities. Although *S. aureus* is the most common pathogen isolated and a considerable proportion is methicillin-resistant *S. aureus* (MRSA), administrating glycopeptide to target this pathogen remains controversial due to conflicting results.[11-13]

Surgical procedures include arthroscopic debridement, open incision and drainage, and needle aspiration. Repeated needle aspiration is performed for limited indications, such as low Gachter stage. However, there is a paucity of studies dealing with the risk factors for the failure of single arthroscopic debridement in the native knee joint. Systemic analysis regarding the failure rate of single arthroscopic reported an average failure rate of 25.5%, but the rate was inconsistent between studies, ranging from 4.9% to 71.8%.[14-17]

Previous studies reported that history of inflammatory arthropathy, high synovial fluid cell count, *S. aureus* infection, early postoperative C-reactive protein (CRP) level, and history of DM are risk factors for failure that can lead to additional surgical procedures, but these factors were not analyzed for each joint.[18,19] Radhamony, et al.[20] reported several risk factors for the failure of single arthroscopic debridement in a native joint, such as CRP, body mass index (BMI), creatinine level, and high neutrophil count. However, these findings were inconsistent with previous studies, and the effect of empirical antibiotics was not considered. Given the inconsistency of risk factors and the paucity of studies regarding septic arthritis of the knee joint, our study aimed to identify the risk factors associated with the failure of single arthroscopic debridement in a native knee joint. We hypothesized that various factors known to affect surgical outcomes of knee joint infection, including high synovial fluid cell count, postoperative CRP, proportion of patients with DM, and *S. aureus* infection, would be significantly higher in patients who failed to eradicate infection with a single arthroscopic surgery.[18-23] Our secondary endpoint was to analyze the efficacy of empirical glycopeptide administration in reducing the risk of additional surgical procedures.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board (IRB) of Yonsei University, Gangnam Severance Hospital, which waived the requirement for informed consent given the retrospective nature of the study (IRB No. 3-2023-0408). Patients who had undergone primary arthroscopic debridement of septic knee arthritis from March 2005 to December 2022 at a single institute were included. Inclusion criteria were as follows: 1) patients who had arthroscopic debridement for septic knee arthritis of the native joint and 2) patients aged over 20 years. Exclusion criteria were as follows: 1) patients with primary surgical treatment conducted at other institutes; 2) patients who received antibiotics before acquiring synovial fluid for analysis; 3) previous history of infection in the ipsilateral knee; and 4) patients for whom infection status could not be evaluated. The study population was divided into group 1 (infection eradication after single arthroscopic debridement) and group 2 (failure of infection eradication after single arthroscopic debridement, leading to additional surgery).

Data of patients' age, BMI, history of injection or surgical procedure on the affected knee, and comorbidities were collected. Regarding laboratory data, liver function was assessed by serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), kidney function by serum blood urea nitrogen (BUN), creatine level, and calculated estimated glomerular filtration rate (eGFR), and general nutritional status by serum protein and albumin; and these evaluations were performed routinely before surgery. In addition, blood white blood cell (WBC) count, serum CRP level, synovial fluid WBC count, and synovial fluid culture were conducted.

Diagnosis

The diagnosis of septic arthritis in the native knee joint was made by considering both clinical symptoms and laboratory results. For patients presenting with clinical symptoms of acute septic arthritis, laboratory tests including synovial fluid analysis and blood WBC, CRP, and erythrocyte sedimentation rate were performed. Among those with symptoms of acute septic arthritis, a diagnosis was made if one or more of the following criteria were met: 1) isolated pathogen in synovial fluid; 2) WBC $>5.0\times10^3$ for synovial fluid analysis; 3) positive Gram stain test for synovial fluid; and 4) suspicion of septic arthritis due to pathologic features in accordance with the modified criteria by Newman, based on the decision of the attending physician at the time of hospitalization.[24-26]

Treatment

Prophylactic antibiotics covering a wide spectrum of microorganisms were administrated after obtaining synovial fluid by

https://doi.org/10.3349/ymj.2024.0190

arthrocentesis. After the culture and drug sensitivity of the isolated pathogen were obtained, the antibiotic regimen was modified in consultation with the infectious disease department. Data of initial empirical IV antibiotics were collected for analysis regarding the efficacy of initial glycopeptide treatment. Vancomycin was administered to patients who required glycopeptide treatment, while teicoplanin was administered at the renal dose for patients who had decreased renal function before or during the administration of vancomycin. For patients with an eGFR above 80 mL/min, a dosage of 12 mg/kg was administered every 12 hours for 2 days, followed by a daily administration of 12 mg/kg. For patients with eGFR between 30 mL/min and 80 mL/min, a half dose was applied, and for patients with eGFR below 30 mL/min, a one-third dose was applied. Routine therapeutic drug monitoring of vancomycin was performed, and the dose was adjusted in consultation with the laboratory medicine department if needed.

Arthroscopic examination was performed using standard anterolateral and anteromedial portals. Visualization of the posteromedial and posterolateral compartments was achieved through the transcondylar notch, and posteromedial or posterolateral portals were created as needed. Given that the neurovascular bundle lies near the posterior compartment, debridement of this area was done with caution.[27] A lateral suprapatellar portal was made for the debridement of the suprapatellar pouch. Massive irrigation, synovectomy, and debridement of devitalized tissue were performed. A wound drainage system was inserted for each compartment. According to the arthroscopic findings, Gachter stage was graded, with stages 1 and 2 defined as low Gachter stage and stages 3 and 4 defined as high Gachter stage.

Assessment of infection eradication

Eradication of infection was defined as improved clinical symptoms accompanied by a normalized acute inflammatory marker, specifically a CRP level below 10 mg/L. Improved clinical symptoms included pain relief and improvement of local infection signs, such as tenderness, localized heat, and redness. Clinical symptoms and serologic markers were routinely assessed. Persistent clinical symptoms or elevation of inflammatory markers were considered indications of failure to eradicate the infection, and additional surgery was performed at the attending surgeon's discretion.

Statistics

For the univariate analysis, two-tailed Student's t-test was conducted. For binary variables, Fisher's exact test was used. Variables with a *p*-value less than 0.2 were included in the multivariate analysis. Stepwise variable selection for a logistic regression model was employed for the multivariate analysis. Statistical analyses were conducted using IBM SPSS statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 134 patients underwent primary arthroscopic debridement for septic arthritis at our institute. Among them, two patients were excluded due to mortality within 1 month after the primary arthroscopic debridement caused by sepsis. Out of the 132 patients who were included in our analysis, 115 (87.1%) were able to eradicate infection with a single arthroscopic surgery. However, 11 patients required one additional surgical debridement, two patients required two additional debridement procedures, and two patients required three additional surgeries. One patient underwent five additional surgical procedures to control the infection. All additional surgical procedures were performed arthroscopically, except for one patient who was diagnosed with osteomyelitis after three arthroscopic debridement surgeries. This patient required additional curettage and antibiotics cement insertion, and ultimately underwent arthrodesis. One patient failed to control the infection with a single surgery and was scheduled for an additional surgical debridement, but was transferred to another institute due to personal circumstances. Gachter stage 2 was the most frequent in group 1, while Gachter stage 3 was most common in group 2. In group 1, 75.0% had low Gachter stage, whereas only 30.8% had low Gachter stage in group 2 (Table 1).

Isolated pathogen

Out of 132 patients, 80 (60.6%) had no pathogens isolated. Among the 28 patients with *S. aureus* infection, eight patients

Table 1. Proportion of Patients for Each Gachter Stage (n=105)

	Group 1 (n=92)	Group 2 (n=13)
1 (n=26, 24.8%)	25 (96.2)	1 (3.8)
2 (n=47, 44.8%)	44 (93.6)	3 (6.4)
3 (n=25, 23.8%)	20 (80.0)	5 (20.0)
4 (n=7, 6.7%)	3 (42.9)	4 (57.1)

Data are presented as n (%).

Table 2. Isolated Pathogens from Synovial Fluid

	Group 1 (n=115)	Group 2 (n=17)	Total
Staphylococcus	26 (22.6)	8 (47.1)	34
MRSA	5 (4.3)	3 (17.6)	8
MSSA	15 (13.0)	5 (29.4)	20
Coagulase-negative *Staphylococcus*	6 (5.2)	0 (0.0)	6
Streptococcus	5 (4.3)	1 (5.9)	6
Group B *Streptococcus*	1 (0.9)	0 (0.0)	1
Streptococcus pneumoniae	1 (0.9)	0 (0.0)	1
Other *Streptococcus*	3 (2.6)	1 (5.9)	4
Pseudomonas aeruginosa	4 (3.5)	1 (5.9)	5
Others	6 (5.2)	1 (5.9)	7
No growth	74 (64.3)	6 (35.3)	80

MRSA, methicillin-resistant S. aureus; MSSA, methicillin-sensitive *S. aureus*.
Data are presented as n (%).

Table 3. Results of Univariate Analysis

	Group 1 (n=115)	Group 2 (n=17)	*p* value
Age (yr)	62.42±16.95	60.82±16.69	0.718
Sex			0.300
Male	51 (44.3)	5 (29.4)	
Female	64 (55.7)	12 (70.6)	
BMI (kg/m^2)	23.46±3.13	23.46±2.94	0.995
Symptom duration (day)	13.57±24.32	16.47±21.77	0.642
History of injection*	26 (22.6)	8 (47.1)	0.041
History of surgery	25 (21.7)	3 (17.6)	0.767
DM*	26 (22.6)	12 (70.6)	<0.001
Osteoarthritis	55 (47.8)	10 (58.9)	0.445
Steroid user	3 (2.6)	0 (0)	>0.999
Immunosuppressant	17 (14.8)	3 (17.6)	>0.999
In-hospital infection	7 (6.1)	1 (5.9)	>0.999
Blood WBC (/μL)	11704.57±6330.02	10971.54 ±3397.28	0.684
Pre op CRP (mg/L)*	122.14±99.84	172.32±148.14	0.073
Synovial fluid WBC >50000/mm^3	82 (71.3)	14 (82.4)	0.362
S. aureus infection	20 (17.4%)	8 (47.1%)	0.010
BUN (mg/dL)	19.39±16.11	17.95±10.74	0.722
Cr (mg/dL)	1.12±1.50	1.50±2.28	0.366
eGFR (mL/min/1.73 m^2)	84.56±30.20	83.76±35.93	0.922
AST (IU/L)	29.83±23.37	28.59±28.47	0.842
ALT (IU/L)	29.33±29.58	31.41±39.46	0.796
Serum protein (g/dL)	6.60±0.81	6.38±0.99	0.306
Serum albumin (g/dL)*	3.49±0.71	3.12±0.93	0.057
HbA1c (DM patients, %)	8.29±2.09	8.36±2.46	0.933
High Gachter stage (stage 3 or 4)†	23 (25.0)	9 (69.2)	0.002

BMI, body mass index; DM, diabetes mellitus; WBC, white blood cell; CRP, C-reactive protein; BUN, blood urea nitrogen; Cr, Creatinine; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
Data are presented as mean±standard deviation or n (%).
*Variables included in multivariate analysis; †Analysis between patients with available data regarding Gachter stage.

had MRSA, and 20 patients had methicillin-sensitive *S. aureus*. The next most common pathogen was Pseudomonas aeruginosa (5/132), followed by *S. epidermidis* (4/132). The proportion of pathogens in each group is detailed below (Table 2).

Univariate analysis

Analysis of continuous variables showed no significant differences in terms of age (p=0.718), BMI (p=0.995), level of BUN (p=0.722), creatine (p=0.366), eGFR (p=0.922), AST (p=0.842), ALT (p=0.796), serum protein level (p=0.306), serum albumin level (p=0.057), initial blood WBC count (p=0.684), and initial serum CRP level (p=0.073). History of DM (22.6% vs. 70.6%, p<0.001), history of injection in the affected knee (22.6% vs. 47.1%, p=0.041), high Gachter grade (25.0% vs. 69.2% p=0.002), and isolation of *S. aureus* (17.4% vs. 47.1%, p=0.010) were identified as binary variables analyzed as risk factors. However, osteoarthritis, synovial WBC count higher than 50000/mm^3, history of surgical treatment on the affected knee, use of immunosuppressant agents, and hospitalization at the time of first symptom showed no significant difference between the two groups (Table 3).

Table 4. Results of Multivariate Logistic Regression Analysis

Variable	Odds ratio (95% CI)	*p* value
DM	12.002 (3.243–44.418)	<0.001
Injection history	4.812 (1.367–16.939)	0.017
S. aureus infection	4.804 (1.282–18.001)	0.031
Preoperative CRP	1.003 (0.998–1.009)	0.297
Preoperative albumin	1.474 (0.661–3.291)	0.634

CI, confidence interval; DM, diabetes mellitus; CRP, C-reactive protein.

Twenty-nine patients were initially treated with IV glycopeptide. There was no significant difference in the proportion of MRSA patients between those treated with initial IV glycopeptide (10.3%, 3/29) and those without (4.9%, 5/103) (p=0.373). Among the patients, 20.9% (24/115) in group 1 were treated initially with IV glycopeptide compared to 11.8% (2/17) in group 2, which showed no significant difference (p=0.530).

Multivariate analysis

Variables identified with p-values less than 0.2 were included in the multivariate analysis. Since the inclusion of Gachter stage led to the exclusion of 20.5% of the patients, Gachter stage was excluded from the multivariate analysis despite significant differences according to the univariate analysis. DM (p<0.001), *S. aureus* infection (p=0.031), and injection on the affected knee (p=0.017) were identified as independent risk factors, showing a 12.002-fold, 4.804-fold, and 4.812-fold increase in risk, respectively. In contrast, serum albumin level and preoperative CRP level showed no significant difference (p=0.634 and 0.297, respectively) (Table 4).

DISCUSSION

Our study identified DM, history of injection, *S. aureus* infection, and high Gachter stage as risk factors for additional surgical procedures for septic arthritis in the native knee joint. The risk of failure was especially high (57.1%) in patients with Gachter stage 4.

Among the factors associated with an increased risk of failure, DM and injection history were the factors related to patient history. DM, which is also reported as a risk factor for septic arthritis, is known to impair immune responses, making it difficult to eradicate infection.[28,29] It is notable that among the failure group, 70.6% had DM compared to only 22.6% in group 1. Despite the high proportion of DM patients in group 2, the mean HbA1c level did not differ between the two groups. Although a previous study by Stratton, et al. reported a linear relationship

https://doi.org/10.3349/ymj.2024.0190

between HbA1c and DM-related complications, recent studies have questioned the clinical benefit of lowering HbA1c.[30,31] Our study also supports this finding, suggesting that patients with a previous history of DM, regardless of their HbA1c level at the time of surgery, should be cautioned about the potential failure to eradicate infection with a single surgical procedure.

The pathophysiology of septic arthritis is known to be associated with multiple factors. Once the pathogen enters the articular space, bacteria adhere to the synovial cells and induce the host to express proteins which could facilitate the pathogen to adhere to the synovium. In addition to this process, *S. aureus* secretes other virulent factors and forms a biofilm.[32] In Gachter stages 3 and 4 joints, which involve thickening of the synovial membrane, damage to cartilage, and bony destruction, there is an increased possibility of biofilm formation in areas that are inaccessible by arthroscopy, which might be an explanation for the increased risk of failure.

There have been inconsistencies in studies regarding treatment modalities for patients with Gachter stages 3 and 4. Balabaud, et al.[14] suggested arthrotomy for Gachter stage 3 patients, while Wirtz, et al.[33] recommended arthroscopic treatment for Gachter stage 3 patients with symptom duration of less than 5 days. Böhler, et al.[24] suggested arthroscopic treatment for Gachter stage 3 patients regardless of symptom duration. In our study, there was no significant difference in the proportion of patients with symptom duration of more than 5 days, and nor in the mean number of days of symptom duration in Gachter stage 3 patients. Therefore, our study concluded that arthroscopic treatment, regardless of symptom duration, should be a treatment option for Gachter stage 3 patients. For Gachter stage 4 patients, previous studies have shown a high rate of infection eradication in Gachter stage 4 septic arthritis with a single open debridement.[24,33] Furthermore, Böhler, et al.[24] reported successful outcomes with single open arthrotomy in all two of their Gachter stage 4 patients. Although it might not be appropriate to directly compare our results with these due to the small sample size, open arthrotomy could potentially be a better treatment option for Gachter stage 4 patients. Further studies examining the success of single surgical procedures with larger number of patients treated with open arthrotomy are needed for a better understanding of optimal treatment selection.

Few studies have revealed the devastating cartilage destruction caused by delayed administration of antibiotics in vitro. Therefore, administrating adequate prophylactic antibiotics before pathogen isolation and antibiotic sensitivity testing is essential. However, there is no consensus on the selection of empirical IV antibiotics. Few studies have shown a growing incidence of MRSA patients.[34] Studies from Boston, Detroit, Northern California, Sao Paolo, and Taiwan showed a 21%–50% incidence of MRSA, and 62% of pediatric musculoskeletal infections in Texas were due to MRSA.[35-40] Given the inferior outcomes associated with MRSA infection, some studies recommended antibiotics covering MRSA.[11,12,41] In contrast, a study by Cipriano, et al.[13] showed a high percentage of antibiotics de-escalation after drug susceptibility testing, advising against the routine administration of glycopeptide as empirical treatment. In light of these conflicting studies, the efficacy of administering glycopeptide as an empirical antibiotic was analyzed. Since there was no significant difference in the proportion of MRSA patients, mean Gachter stage, and CRP level between patients who initially received glycopeptide and those who did not, the severity of infection was not significantly different. Without a difference in the severity of infection, the failure rate also did not show any difference between the glycopeptide group and the non-glycopeptide group. Therefore, our study concluded that glycopeptide did not provide a benefit in reducing the risk of additional surgery. Given the risk of antibiotics resistance and complications such as acute kidney injury, the routine administration of glycopeptide as an empirical antibiotic should be considered carefully. Rather than routine administration of glycopeptide, emphasis on early detection using various techniques would lead to a better decision regarding the selection of appropriate antibiotics.[42] Our institute had administrated glycopeptide as an empirical antibiotic for patients with high risk of MRSA, such as those with hospital-acquired infections and infections associated with intra-articular allograft or fixation devices. Further studies with a higher level of evidence are needed to compare the effect of glycopeptide as an empirical antibiotic for eradicating infection in septic arthritis of the native knee joint.

Previous studies have investigated the failure of arthroscopic debridement for septic arthritis of the native joints. A high CRP level, which is a valuable tool for screening infection, was reported to be a risk factor in both the preoperative and postoperative periods.[19,20,43] To our knowledge, the study by Radhamony, et al.[20] was the only study that analyzed the risk factors specifically for the knee joint. They reported CRP, BMI, creatinine levels, and high neutrophil count as risk factors, while DM and high Gachter stage had no significant effect. Both the risk factors and the failure rate were inconsistent with our study's findings (12.9% vs. 39.7%). It is notable that the mean time from initial debridement to the second surgical procedure was 3.96 days in the study by Radhamony, et al.,[20] while the median time was 21 days in our study. This relatively short period for deciding on a second surgical procedure could be a possible explanation for the relatively high failure rate compared to our study. Although it is difficult to specify an exact duration for determining failure, we suggest that the timing for deciding on an additional surgical procedure should differ between patients who have the risk factors reported in our study and those without, to avoid premature decisions and unnecessary surgical procedures.

This study had several limitations. First, due to the lack of data about arthroscopic findings for surgeries performed before the electronic medical record system was established, Gachter stage was unable to identify. Second, this was a retro-

spective study and could not exclude certain biases. Third, this study included patients from four different physicians, and the possibility of bias from this limitation should be considered. However, by doing so, our study has the strength of analyzing septic arthritis specifically in the native knee joint, considering that each joint has its unique structure.

In conclusion, comorbidity of DM, history of previous injection, isolated *Staphylococcus aureus* in synovial fluid, and high Gachter stage were associated with a higher risk of failure to eradicate infection with a single arthroscopic procedure, whereas history of arthropathy, preoperative CRP level, preoperative blood WBC count, and synovial fluid neutrophil count had no significant relation. Empirical glycopeptide administration also showed no significant benefit in reducing the risk of additional surgical procedures for infection control.

AUTHOR CONTRIBUTIONS

Conceptualization: Junwoo Byun and Sung-Hwan Kim. Data curation: Junwoo Byun, Kwangho Chung, Se-Han Jung, and Hyeokjoo Jang. Formal analysis: Junwoo Byun. Funding acquisition: Sung-Hwan Kim. Investigation: Junwoo Byun and Sung-Hwan Kim. Methodology: all authors. Project administration: Sung-Hwan Kim. Resources: Chong-Hyuk Choi, Min Jung, and Sung-Hwan Kim. Software: Junwoo Byun. Supervision: Sung-Hwan Kim. Validation: all authors. Visualization: Junwoo Byun. Writing—original draft: Junwoo Byun. Writing—review & editing: Chong-Hyuk Choi, Min Jung, Kwangho Chung, Se-Han Jung, and Sung-Hwan Kim. Approval of final manuscript: all authors.

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