

Antimicrobial stewardship without infectious disease physician for patients with candidemia: A before and after study

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Abstract

Background: Little is known about the effects of antimicrobial stewardship team (AST) without infectious disease physician (IDP) on clinical outcome in patients with candidemia.

Methods: We conducted a before and after study involving patients with hospital-acquired candidemia at a tertiary hospital without IDPs. The AST consisted of physicians, pharmacists, nurse, microbiologist, and administrative staff. A candidemia care bundle was developed based on the Infectious Disease Society of America (IDSA) guideline. The non-IDP AST provided recommendations to the attending physicians whose patients developed candidemia during hospitalization. The primary outcome was 30-day all-cause mortality, while the secondary outcomes were adherence to the IDSA guidelines regarding the management of candidemia. Data of up to 3 years of preintervention and 3 years of intervention period were analyzed.

Results: By 30 days, 11 of 46 patients (23.9%) in the intervention group and 7 of 30 patients (23.3%) in the preintervention group died (adjusted hazard ratio for the intervention group: 0.68 [95% CI 0.24-1.91]). The non-IDP AST was associated with appropriate empirical antifungal therapy (100% vs 60.0%; proportion ratio 1.67 [95% CI 1.24-2.23]), appropriate duration of treatment (84.7% vs 43.3%; 1.96 [1.28-3.00]), removal of central venous catheters (94.4% vs 70.8%; 1.33 [1.02-1.74]), and ophthalmological examination (93.5% vs 63.3%; 1.48 [1.12-1.96]).

Conclusions: Although we found no significant difference in 30-day mortality, the non-IDP AST was associated with improved adherence to guidelines for management of candidemia.

KEYWORDS

antimicrobial stewardship, bundle, candidemia, infectious disease physician

1 | INTRODUCTION

Candidemia is a growing problem in healthcare settings in many countries worldwide.¹ A recent study conducted in 183 US medical centers showed that *Candida* species have become the most commonly identified pathogens in nosocomial bloodstream infections.² Despite advances in the recognition of high-risk patients with candidemia and antifungal agents, the reported overall mortality due to candidemia is very high, ranging from 25% to 72%.³⁻¹⁴ Moreover, inappropriate therapy for systemic *Candida* infection imposes a heavy economic burden mainly due to prolonged hospital stay and overall use of hospital resources.^{15,16}

Appropriate empirical antifungal therapy and source control are required to reduce mortality in patients with candidemia.^{4-7,16,17} Although the Infectious Disease Society of America (IDSA) updates the clinical practice guidelines for the management of candidiasis every several years to help physicians use antifungal agents appropriately,¹⁸⁻²⁰ such updates have not always led to changes in clinical behavior in a timely fashion. Previous studies demonstrated that 88.9% of patients with candidemia received inappropriate treatment¹⁶ and that the overall rate of adherence to recommendations for the use of antifungal agents was 40% even in a tertiary care hospital,²¹ emphasizing the need to narrow the gap between clinical evidence and bedside practice.

Infectious disease specialists and antimicrobial stewardship teams (AST) have helped encourage the integration of evidence-based treatment into bedside practice. Meta-analyses suggest that consultation with infectious disease specialists for patients with *Staphylococcus aureus* bloodstream infection was associated with improved patient management.^{22,23} Other meta-analyses found that antimicrobial stewardship interventions were effective in reducing carbapenem consumption and mortality.^{24,25} However, it is not uncommon not only in Japan but also in other countries for rural hospitals to have vacancies for infectious disease physicians (IDPs), mainly due to shortages of IDPs. Thus, little is known about the impact of non-IDP AST on clinical outcome of patients with candidemia. The aim of this study was to evaluate the impact of non-IDP AST on candidemia. We hypothesized that the presence of the AST at our facility was associated with lower mortality among patients with candidemia even if the team does not include IDPs.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

We conducted a before and after study of episodes of hospital-acquired candidemia between November 2006 and October 2012. Because we started this project on November 2009, data of up to 3 years of preintervention and 3 years of intervention period were compared. The setting was Saku Central Hospital, located in Nagano Prefecture, Japan. Although Saku Central Hospital is more than 600-bed rural tertiary hospital, no IDPs had ever worked in the facility. In our study, we defined IDPs as infectious disease specialists or physicians who

were primarily engaged in the management of infectious diseases even if they were not specialists. All cases of infectious diseases including bacteremia and candidemia were clinically managed by the attending physicians who were not IDPs. All study procedures were approved by the Institutional Review Boards of Saku Central Hospital.

2.2 | Patients

All hospitalized patients aged ≥ 18 years who developed candidemia during the study period were entered into the study. We defined an episode of candidemia as isolation of *Candida* spp. in at least one blood culture in a patient with clinical signs and symptoms of infection. Episodes were considered to be separate if they were caused by different species or occurred at least 30 days apart, with resolution of clinical features of infection and at least one negative blood culture during the treatment period.²⁶ Patients were excluded if they were on comfort care or on do-not-resuscitate (DNR) order.

2.3 | Antimicrobial stewardship team

Participation in the AST was voluntary and open to any physician and clinical staff at our hospital. To implement a multidisciplinary team approach, the team comprised 13 members: 2 nephrologists, 2 surgeons, 1 general practitioner, 1 emergency physician, 1 gastroenterologist, 1 ophthalmologist, 2 pharmacists, 1 nurse, 1 microbiologist, and 1 administrative staff. The team did not include any IDPs. At the first in-person meeting held in March 2009, members of the interdisciplinary AST shared evidence supporting various recommended practices for management of candidemia. During the next several months, the AST developed a candidemia care bundle based on the IDSA guideline.¹⁹ The bundle consisted of six key elements: appropriate empirical selection of antifungals, appropriate empirical dosaging of antifungals, appropriate duration of treatment, removal of existing central venous catheters (CVC), follow-up blood cultures until clearance of candidemia, and ophthalmological examination (Table 1). Micafungin was selected

TABLE 1 Bundle elements in patients with candidemia

Appropriate empirical selection of antifungals

Appropriate empirical dosaging of antifungals:

micafungin 100-150 mg daily

lipid formation of amphotericin B 3-5 mg/kg daily

voriconazole 400 mg (6 mg/kg) bid for 2 doses, then 200 mg (3 mg/kg) bid

fluconazole 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily

Treatment for 14 d after first negative blood culture result and resolution of signs and symptoms associated with candidemia

Removal of existing central venous catheters

Follow-up blood cultures until clearance of candidemia

Ophthalmological examination

bid, twice a day.

as the empirical antifungal therapy, based on the IDSA guideline and its effectiveness for any potential fluconazole-resistant *C. glabrata* and *C. krusei*, both of which have been previously identified at our hospital. However, the regimen was changed depending on the patient general condition, comorbidity, drug-drug interaction, and clinical laboratory test results as needed. Based on the understanding of the team members of the project and the time frame that had been targeted for intervention implementation, November 2009 was selected as the start of the intervention time frame for analysis.

When the Gram stain revealed yeast consistent with *Candida* spp. from a positive blood culture, the staff of the microbiological laboratory informed the attending physician immediately by telephone during the preintervention and intervention periods. In addition, the AST members also received real-time notification of positive culture results during the intervention period. This notification was via e-mail and telephone for cases identified on Monday through Saturday from 08:00 to 17:00. After-hours results were reviewed by the microbiological laboratory personnel the following business day. Then, a physician became the person in charge of the case and directly contacted the attending physician in charge of the patient, to discuss the management of candidemia and made prospective recommendations in accordance with the bundle until the patient was discharged from the hospital or died. The entire AST shared information about the patients with candidemia and the clinical course during the intervention period and discussed appropriate management online. For smooth integration of our recommendations into bedside clinical practice based on the needs of the attending physicians, we paid strict attention to communication with the attending physicians. When a patient from the Department of Surgery developed candidemia, the surgeon member of the AST became in charge of the patient. However, our recommendations were deferred to the discretion of the attending physicians. The project lasted 3 years due to shortage of physicians in our team. Thus, for analysis purposes, the preintervention period was defined as November 2006 through October 2009, and the intervention period, as November 2009 through October 2012.

2.4 | Data collection

The baseline characteristics of each study patient were recorded when blood culture was identified as positive for *Candida* species. These included age, gender, race, intensive care unit (ICU) stay, the hospital ward, and comorbidities at the time of diagnosis of candidemia. The infection-related characteristics examined in this study included the use of CVC, use of parenteral nutrition, immunocompromised status at time of diagnosis, administration of broad-spectrum antibiotics and surgery within 30 days of candidemia diagnosis, infection source, and pathogen species. All cases of candidemia were identified during the preintervention period through the microbiological laboratory database, and all patients clinical and test data were obtained from the electronic or paper medical records.

2.5 | Outcomes

The primary outcome was 30-day all-cause mortality. Survival was defined as the time from the first day of positive blood culture for *Candida* spp. until death, loss to follow-up, or maximum of 30 days. The secondary outcomes focused on adherence to the IDSA guidelines for management of candidemia: appropriate empirical antifungal therapy, appropriate duration of treatment, removal of CVC, and ophthalmological examination.

Outcomes were classified as appropriate if practiced in accordance with the IDSA guidelines for the management of candidemia.^{18,19} Appropriate empirical antifungal therapy was defined as both appropriate choice and dose of the antifungal agent. Our assessment also took into account adjustment for renal and hepatic functions. Because the IDSA practical guideline was updated in 2009, all secondary outcomes were limited to the elements that were based on both guidelines. CVC removal was considered to have been conducted appropriately if all catheters were removed. Ophthalmological examination indicated referrals to an ophthalmology specialist for examination for endophthalmitis during the treatment period. All outcomes were confirmed by the medical records.

2.6 | Microbiological techniques

Candida spp. were isolated from blood specimens using an automated broth microdilution system (BacT/ALERT 3D; BioMérieux Industry, France) and identified using standard techniques. Unfortunately, the microbiological laboratory at our hospital did not perform antifungal susceptibility testing on a routine basis during the preintervention period.

2.7 | Statistical analysis

The baseline characteristics of the patients were expressed as frequencies for categorical variables and median (interquartile range) (IQR) for continuous variables. We used Fisher's exact test and Mann-Whitney U test to determine the significance of differences between two groups.

For the primary analysis, the time-to-event analysis was performed using the Kaplan-Meier method, and survival curves between the groups were compared using the log-rank test. The multivariable Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence interval (95% CI). The outcome was adjusted for age, gender, recent surgery, ICU admission, immunocompromised status, bacteremia, chronic kidney disease, chronic heart disease, and malignancy at baseline.^{4-8,10,17} Due to the relatively high numbers of covariates that needed to be adjusted for, compared with the number of outcomes, we also used the propensity score method. First, we calculated the propensity scores to estimate the probability that the caring physicians would receive recommendations from the non-IDP AST using a multivariate logistic regression model that contained all the covariates listed above.

Then, the scores were directly incorporated into the statistical models to balance for potential confounders.

For the secondary analysis, the Fisher's exact test was used to compare between-group differences. Proportion ratios were reported with 95% CI without adjustment. All tests were two-tailed, with differences reported as significant when the *P* value was less than .05. Statistical analyses were performed with STATA statistical software, version 13.0 (STATA Corporation, College Station, TX, USA).

3 | RESULTS

3.1 | Participants

During the evaluation period, a total of 78 consecutive patients developed candidemia and none was lost to follow-up. Among these patients, 2 had a DNR order. For the remaining 76 patients included in the analysis, the median age was 74 years (IQR 64-82), with 30 (39.5%) females (Table 2). Malignancy was the most common underlying condition, while neutropenia was rare (1.3%). The majority of patients (*n* = 60; 78.9%) had a CVC in place at the time of diagnosis of candidemia. *C. albicans* was the most common spp. isolated (*n* = 30, 39.5%), followed by *C. parapsilosis* (*n* = 20, 26.3%) and *C. glabrata* (*n* = 18, 23.7%). The baseline characteristics were different between the two groups; patients of the intervention group were significantly more likely to have chronic kidney disease (stage V) compared with those of the preintervention group. Although not significant, a larger number of patients in the intervention group were admitted to the ICU at the time of diagnosis of candidemia.

3.2 | Primary outcome

Of the intervention group, 7 of 30 patients (23.3%) died by 30 days, compared with 11 of 46 patients (23.9%) of the preintervention group (unadjusted HR for the intervention group 1.05 [95% CI 0.41-2.72]; *P* = .91; Table 3). The Kaplan-Meier curves demonstrated that the likelihood of survival was not better for patients receiving recommendations for treatment of candidemia compared to patients not receiving recommendations (Figure 1). However, the result changed after propensity score adjustment (adjusted HR 0.68 [95% CI 0.24-1.91]; *P* = .46), although the difference remained statistically insignificant.

3.3 | Secondary outcomes

Among patients with candidemia, those of the intervention group were significantly more likely to receive appropriate empirical antifungal therapy compared to those of the preintervention group (100% vs 60.0%; proportion ratio 1.67 [95% CI 1.24-2.23]; *P* < .001; Table 4). Five patients (16.7%) of the preintervention group did not receive any antifungal treatment. The remaining 7 empirical antifungal therapies used by the preintervention group were classified as inappropriate for the following reasons: disregard for the recommended choice of antifungal agents in 3 cases and insufficient dosage in 4 cases. The duration of treatment for candidemia was more appropriate in a

significantly larger percentage of patients of the intervention group (84.7% vs 43.3%; 1.96 [1.28-3.00]; *P* < .001). Among 60 patients with CVC, the proportion of patients who had the catheter removed following identification of a positive blood culture was significantly higher in the intervention group (94.4%) than the preintervention group (70.8%) (proportion ratio 1.33 [1.02-1.74]; *P* = .012). Furthermore, more patients of the intervention group underwent ophthalmological examination (93.5% vs 63.3%; 1.48 [1.11-1.96]; *P* < .001).

4 | DISCUSSION

For patients with candidemia, our study showed that recommendations provided by the non-IDP AST through implementation of a therapeutic management bundle did not improve prognosis. However, we found substantial project-associated increases in adherence to the IDSA guidelines for management of candidemia. These results are important because this study was conducted at a tertiary hospital in which no IDPs provided clinical service. Although antimicrobial stewardship programs should be organized by an interdisciplinary team led by an infectious disease specialist,²⁷ our results suggested that non-IDP AST could provide advice to the attending physician on treatment of candidemia in accordance with the guidelines.

To reduce the mortality rate in candidemia through the seamless integration of our recommendations into clinical practice, we implemented a multidisciplinary team approach^{28,29} and an evidence-based bundle based on antimicrobial stewardship programs.^{30,31} However, only 76.1% of the patients of the intervention group survived, with no significant difference in the survival rate between the two groups. There are several likely explanations. First, the severity of illness and comorbidities is known to be associated with mortality.⁷ Second, because delayed use of appropriate antifungal therapy is an independent predictor of hospital mortality in candidemia,⁴⁻⁶ it is possible that the diagnosis was established at a late stage of the disease when patients were less likely to respond to antifungal therapy. Therefore, we need to promote not only our project but also education of the clinical staff at our hospital to enhance antimicrobial stewardship.³²

The implementation of bundles, which is concordant with guidelines, is reported to be effective in the field of infectious diseases. According to a meta-analysis on prevention of surgical site infection (SSI), a bundle comprising nasal decolonization and glycopeptide prophylaxis for patients with colonization of methicillin-resistant *Staphylococcus aureus* (MRSA) was associated with lower rates of SSI (pooled relative risk 0.41 [95% CI 0.30-0.56]).³³ Two large multicenter studies reported that bundled interventions were associated with a decrease in healthcare-associated infections, such as catheter-related bloodstream infections and MRSA infections.^{34,35} Similarly, it has been reported that a national educational effort to promote bundles of care for severe sepsis and septic shock was associated with lower hospital mortality (44.0% vs 39.7%; *P* = .04).³⁶ Our project that used the bundle approach was considered useful in narrowing the gap between clinical evidence and bedside practice even in an IDP-lacking hospital.

TABLE 2 Baseline characteristics

Characteristics	Intervention group (2009-2012) (n = 46)	Preintervention group (2006-2009) (n = 30)	P value
Age, median (IQR), range, years	75 (66-83), 37-92	73 (64-79), 30-86	.21
Female gender, n (%)	17 (37.0)	13 (43.3)	.64
Race, Asian, n (%)	46 (100)	30 (100)	-
ICU admission ^a , n (%)	19 (41.3)	7 (23.3)	.11
Division of admission, n (%)			
Surgery			
Abdominal surgery	10 (21.7)	9 (30.0)	.42
Nonabdominal surgery	7 (15.2)	3 (10.0)	.51
Internal medicine	25 (54.3)	17 (55.2)	.84
Other	2 (4.4)	1 (3.3)	1.00
Underlying disease ^{a,b} , n (%)			
Diabetes mellitus	12 (26.1)	6 (20.0)	.59
Chronic kidney disease (stage V)	11 (23.9)	1 (3.3)	.022
Liver cirrhosis	2 (4.4)	1 (3.3)	1.00
Chronic heart disease (NIHA IV)	6 (13.0)	1 (3.3)	.23
Chronic obstructive pulmonary disease	2 (4.4)	1 (3.3)	1.00
Bacteremia	8 (17.3)	6 (20.0)	.77
Malignancy	18 (39.1)	10 (33.3)	.61
Organ transplant	0 (0)	0 (0)	-
Other risk factors ^b , n (%)			
Central venous catheter ^a	36 (78.3)	24 (80.0)	1.00
Broad-spectrum antibiotics ^c	40 (87.0)	23 (76.7)	.35
Recent surgery ^c	29 (63.0)	17 (56.7)	.64
Parenteral nutrition ^a	23 (50.0)	17 (56.7)	.64
Immunocompromised status ^a , n (%)			
Neutropenia (<500 cells/ μ L)	1 (2.2)	0 (0)	1.00
Chemotherapy	4 (8.7)	5 (16.7)	.31
Immunosuppressive therapy	7 (15.2)	3 (10.0)	.73
Radiotherapy	1 (2.2)	0 (0)	1.00
HIV infection	0 (0)	0 (0)	-
Infection source, n (%)			
Blood	42 (91.3)	27 (90.0)	1.00
Gastrointestinal	0 (0)	2 (6.7)	.15
Urinary	2 (4.4)	1 (3.3)	1.00
Other	2 (4.4)	0 (0)	.52
Previous azole prophylaxis, n (%)	5 (10.9)	5 (16.7)	.50
<i>Candida</i> species, n (%) ^d			
<i>C. albicans</i>	19 (41.3)	11 (36.7)	.81
<i>C. parapsilosis</i>	10 (21.7)	10 (33.3)	.30
<i>C. glabrata</i>	11 (23.9)	7 (23.3)	1.00
<i>C. tropicalis</i>	1 (2.2)	2 (6.7)	.56
<i>C. krusei</i>	2 (4.4)	1 (3.3)	1.00
Other <i>Candida</i> species	5 (10.9)	0 (0)	.15

HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; NYHA, New York Heart Association.

^aPresent at time of diagnosis of candidemia.

^bPatients with more than one underlying condition and risk factor.

^cPresent within 30 d of diagnosis of candidemia.

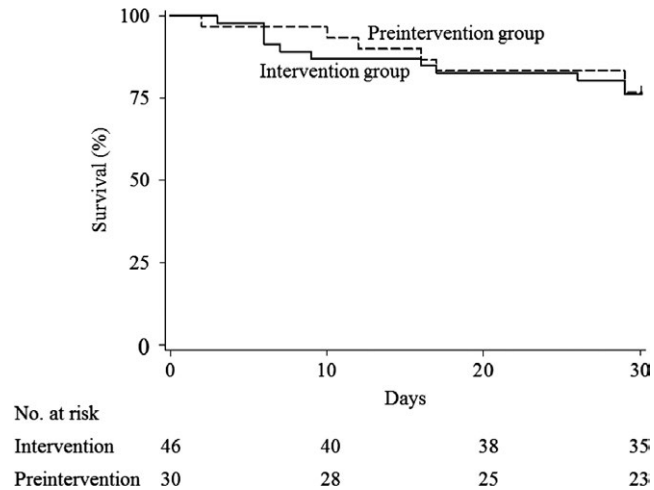
^dThree patients harbored two different *Candida* species, as confirmed by blood cultures.

TABLE 3 Comparison of mortality between the preintervention and intervention groups

Primary outcome	Intervention group (2009-2012) n = 46, n (%)	Preintervention group (2006-2009) n = 30, n (%)	Hazard ratio (95% CI)			
			Unadjusted	P value	Adjusted	P value
Mortality at 30 d	11 (23.9)	7 (23.3)	1.05 (0.41-2.72)	.91	0.68 (0.24-1.91) ^a	.46

CI, confidence interval.

^aAdjusted for a propensity score comprising age, gender, recent surgery, ICU admission, immunocompromised status, bacteremia, chronic kidney disease, chronic heart disease, and malignancy at baseline.

**FIGURE 1** Kaplan-Meier estimates of survival

One of the main aspects of our study is that we suggested the beneficial impact of the non-IDP AST on adherence to the guidelines for management of candidemia. To our knowledge, this is the first report to suggest the association between the non-IDP AST and improved adherence to the guidelines not only in patients with candidemia but also in those with other infectious diseases. Although in general, the IDP-based AST is the best approach to integrate evidence-based treatment into bedside practice,^{24,25} even IDP-based AST seems to have limited value on improvement of prognosis of patients with candidemia.³⁷⁻³⁹ Only a “before and after” study that evaluated the effect of active intervention by the IDP-based AST reported a significant decrease in the 30-day mortality rate from 56% to 22%.³⁸ However, multivariate analysis was not conducted to adjust for confounding variables and the sample size was smaller than that of our study. Given that there remain many IDP-lacking hospitals

worldwide, it is noteworthy that even the non-IDP AST was associated with improved management of patients with candidemia.

Apart from the above strong points, there are several important limitations to our study that should be mentioned. First, similar to other studies that evaluated the effect of an evidence-based bundle of interventions on reduction in healthcare-associated infections,^{34,35} we could not randomize patients with candidemia to receive the intervention or not. Whereas propensity score adjustment can effectively adjust for the observed baseline differences between the intervention and preintervention groups, it cannot adjust for unmeasured confounding factors. Therefore, it is possible that we overestimated the effect of our project.⁴⁰ Second, although the multivariate Cox regression model for survival analysis could have helped us understand the impact of our protocol, the sample size was too small to detect significant reduction in mortality. Third, the IDSA guidelines were revised during the preintervention period. It was important to define only the common elements of the two guidelines as secondary outcomes. Fourth, we did not perform routine measurements of minimum inhibitory concentrations for various antifungal agents used for treatment of fungal infections nor did we assess antifungal susceptibility. Fifth, we did not assess any potential adverse outcomes associated with the non-IDP AST. However, at least the activity of our team was never rejected by the attending physicians. Finally, another limitation is related to external validity, in particular, the single-center design. This may limit generalization of our findings, although we developed our project simply based on the IDSA guidelines.

5 | CONCLUSIONS

Among patients with *Candida* spp.-positive blood cultures, the non-IDP AST was not associated with improved 30-day mortality.

TABLE 4 Comparison of adherence to the guidelines between the preintervention and intervention groups

Secondary outcomes	Intervention group (2009-2012) n/N (%)	Preintervention group (2006-2009) n/N (%)	Proportion ratio (95% CI)	
			Unadjusted	P value
Appropriate empirical antifungal therapy	46/46 (100)	18/30 (60.0)	1.67 (1.24-2.23)	<.001
Appropriate duration of treatment	39/46 (84.7)	13/30 (43.3)	1.96 (1.28-3.00)	<.001
Removal of central venous catheter	34/36 (94.4)	17/24 (70.8)	1.33 (1.02-1.74)	.012
Ophthalmological examination	43/46 (93.5)	19/30 (63.3)	1.48 (1.11-1.96)	<.001

CI, confidence interval.

However, the project significantly improved adherence to the guidelines for management of candidemia. With increased attention to antimicrobial stewardship programs, identifying an appropriate management for candidemia is essential even in hospitals lacking IDPs. We believe that this project may have the potential to narrow the gap between clinical evidence and bedside practice even in a hospital in which IDPs do not provide clinical service worldwide. Further studies are warranted to confirm the effects of similar non-IDP ASTs in a multicenter setting.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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