Frequency of Acute Kidney Injury in Patient Receiving Piperacillin - Tazobactam: A Hospital-based Study from Qatar

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ABSTRAK

Latar belakang: *beberapa penelitian telah melaporkan acute kidney injury (AKI) terkait piperacillin-tazobactam (TAZ/PIPC) dengan berbagai frekuensi. Tujuan dari penelitian ini adalah menentukan frekuensi AKI terkait TAZ/PIPC di antara pasien kami dan untuk mengidentifikasi faktor risiko pada entitas klinis.* ***Metode:*** *penelitian potong lintang retrospektif ini dilakukan di Rumah Sakit Umum Hamad; melibatkan pasien dewasa yang dirawat dari Januari 2017 hingga Desember 2017.* ***Hasil:*** *terdapat 917 pasien yang diikutsetakan, di antaranya 635 (69,25%) laki-laki dan 282 (30,75%) perempuan. Usia rerata pasien adalah 52 (SB 19) tahun, dan 98 (10,7%) pasien didiagnosis dengan AKI. Para pasien dengan AKI secara signifikan lebih tua daripada tanpa AKI [59,71 (SB 19,79) versus 51,06 (SB 18,67); P <0,001]. Setelah inisiasi TAZ/PIPC, rerata kadar kreatinin pada kelompok AKI lebih tinggi dibandingkan rerata kadar kreatinin pada kelompok non-AKI, [158,91 (SB 81,93) berbanding 66,78 (SB 21,42); P<001]. Rerata waktu timbulnya AKI setelah inisiasi PIPC/TAZ adalah 4,46 (SB 3,20) (1-12 hari). AKI secara signifikan terkait dengan albumin serum rata-rata rendah (P<0,001), gula darah puasa rerata tinggi (P<0,001), penyakit arteri koroner (P<0,001), gagal jantung (P<0,001), penyakit hati (P=0,047), diabetes melitus (P=0,021) dan hipertensi (P<0,001). Angka mortalitas di rumah sakit secara signifikan lebih tinggi pada kelompok AKI [38,78% berbanding 5,13% pada kelompok non-AKI; P<0,001], dan hanya usia lanjut dan gagal jantung yang ditemukan sebagai faktor risiko independen untuk AKI terkait TAZ/PIPC.* ***Kesimpulan:*** *TAZ/PIPC secara signifikan berhubungan dengan AKI. Usia lanjut dan gagal jantung diidentifikasi sebagai faktor risiko independen untuk AKI terkait TAZ/PIPC.*

Kata kunci: *acute kidney injury, piperacillin/tazobactam, usia lanjut, gagal jantung.*

ABSTRACT

Background*: several studies have been reported piperacillin-tazobactam (TAZ / PIPC)-associated AKI with various frequencies. The aim of this study was to determine the frequency of TAZ/PIPC- associated AKI among our patients and to identify the risk factors for this clinical entity.* ***Methods:*** *this retrospective cross-sectional study was conducted at Hamad General Hospital; it involved adult patients who were admitted from January 2017 to December 2017.* ***Results:*** *we involved 917 patients, of whom 635 (69.25%) were males and 282 (30.75%) were females. The mean age of the patients was 52 (SD 19) years, and 98 (10.7%) patients were diagnosed with AKI. The patients with AKI were significantly older than without AKI [59.71 (SD 19.79) versus 51.06 (SD 18.67); P <0.001]. After TAZ/PIPC initiation, the mean creatinine level in the AKI group was higher than the*

mean creatinine level in the non-AKI group, [158.91 (SD 81.93) versus 66.78 (SD 21.42); P<001]. The mean time of onset of AKI after PIPC/TAZ initiation was 4.46 (SD 3.20) (1-12 days). AKI was significantly associated with low mean serum albumin (P<0.001), high mean fasting blood glucose (P<0.001), coronary artery diseases (P<0.001), heart failure (P<0.001), liver diseases (P=0.047), diabetes mellitus (P=0.021) and hypertension (P<0.001). The in-hospital mortality was significantly higher in the AKI group [38.78% versus 5.13% in the non-AKI group; P<0.001], and only advanced age and heart failure were found as independent risk factors for TAZ/PIPC-associated AKI. ***Conclusion:*** *TAZ/PIPC was significantly associated with AKI. Advanced age and heart failure were identified as independent risk factors for TAZ/PIPC-associated AKI.*

Keywords: *acute kidney injury, piperacillin/tazobactam, advanced age, heart failure.*

INTRODUCTION

The combination piperacillin-tazobactam (TAZ/PIPC) is a commonly prescribed empirical therapy for patients with healthcare-associated infections, as it provides coverage against both methicillin-sensitive *Staphylococcus aureus* (MSSA) and *Pseudomonas aeruginosa*.[1]

Common adverse effects include headache, trouble sleeping, itching, skin rash, nausea, leucopenia, neutropenia, constipation, and diarrhea.[1] Serious adverse effects include Clostridioides difficile infection and allergic reactions including anaphylaxis may occur.[2,3] Acute kidney injury (AKI) as an adverse effect of TAZ/PIPC has been mentioned in several reports with varying frequencies. The proposed mechanisms for TAZ/PIPC induced AKI include acute interstitial nephritis or toxic effects on the renal tubule.[4-5]

During our practice, we noted that many patients developed AKI after using TAZ /PIPC; however, the frequency of this complication in our hospital is unknown. This study was designed to determine the frequency of AKI due to TAZ/PIPC among our patients and to identify the risk factors for TAZ/PIPC-associated AKI.

METHODS

This retrospective analytical cross-sectional study was conducted at Hamad General Hospital (HGH), which is a tertiary center that covers all specialties except for hematology-oncology and obstetrics. This study involved adult patients who were admitted to HGH from January 1, 2017 to December 31, 2017 and received piperacillin-tazobactam at a dose of 4.5 g intravenously every eight hours daily.

Inclusion and Exclusion Criteria

Eligible subjects were adults of 18 years of age or more, who were admitted to HGH from January 1, 2017 to December 31, 2017, and received piperacillin-tazobactam at a dose of 4.5 g intravenously every eight hours daily. Patients younger than 18 years old and patients who had a baseline serum creatinine level of ≥1.2 mg/dl (106 mcmol/L) [3] or receiving renal replacement therapy at the time of the initiation of treatment, were excluded. Moreover, patients who had recent administration of contrast agents also were excluded.

Source of Data and Data Collection

The list of the patients who received TAZ/PIPC from January 1, 2017 to December 31, 2017 was obtained from the pharmacy electronic records at HGH. Then the electronic medical records (Cerner system) of all patients were screened for inclusion purposes and the records of the eligible patients were reviewed to obtain demographic data, Laboratory data (baseline serum creatinine, serum creatinine after receiving TAZ/PIPC, fasting blood glucose and serum albumin), comorbidities (hypertension, CAD, DM, COPD, PAD, heart failure, liver disease, active cancer), concomitant drugs (NSAIDS, ACE/ARB, vancomycin, acyclovir, diuretics), type of infection and the outcome.

Outcomes

The primary outcome of our study was acute kidney injury (AKI), which was defined according to the KDIGO (Kidney Disease: Improving Global Outcomes) criteria, [6] as an increase in serum creatinine level by 50% or higher from baseline or by 0.3 mg/dL (26.5 μmol/L) or higher within 2 hospital days or

fewer. The secondary outcome was in-hospital mortality, which was defined as all deaths occurring during the hospital stay.

Data Analysis

Results were expressed as mean ± SD. After the demonstration of a normal distribution, two-tailed unpaired Student's t-tests and the Mann-Whitney test were used to compare the distribution of quantitative variables and the $\chi 2$ tests and Fisher's test for categorical variables. Variables that showed significant association in bivariate analysis (P<0.05) were entered into multivariate analysis to identify the independent risk factors of AKI at P<0.05.

Ethical Approval

The ethical approval for this study was obtained from the medical research committee (MRC) at Hamad Medical Corporation (HMC). The reference to the approved proposal was MRC-01-18-065. According to the MRC, a waiver of informed consent is not required for any retrospective study and all data/samples were fully anonymized by the principal investigator and other team members before being accessed by others including the biostatistician, journal and readers.

RESULTS

During the study period, we retrospectively identified 2540 patients who received TAZ/PIPC, of which 917 fulfilled the inclusion criteria and became the subject of this study as illustrated in **Figure 1**. The electronic medical records of all eligible patients were fetched and reviewed. Of the 917 patients, there were 635 (69.25%) males and 282 (30.75%) females. The mean age of the patients was 52 SD 19 (range:18-90 years) and 98 (10.7%) patients were found to have acute kidney injury (AKI). **Table 1** describes the demographic and clinical data of the cohort of this study.

A Comparison between AKI and Non-AKI Groups

The patients with AKI were significantly older than without AKI [59.71 (SD 19.79) vs 51.06 (SD 18.67); P <0.001]. After TAZ/PIPC initiation, the mean creatinine level in the AKI group was higher than the mean creatinine level in the non-AKI group, [158.91 (SD 81.93) versus 66.78 (SD 21.42); P<001]. The mean time of onset of AKI after PIPC/TAZ initiation was 4.46 (SD 3.20) (1-12 days). AKI was significantly associated with low mean serum albumin (P<0.001), high mean fasting blood glucose (P<0.001), coronary artery diseases (P<0.001), heart failure (P<0.001), liver diseases (P=0.047), diabetes mellitus (P=0.021) and hypertension (P<0.001). The in-hospital mortality was

Table 1. Demographic and Clinical Characteristics of the Patients Involved in This Study.

Characteristics	Number (%) / Mean (SD)
Sex, n (%)	
- Female	282 (30.75)
- Male	635 (69.25)
Age (years), mean (SD)	51.98 (18.97)
BMI, mean (SD)	27.04 (6.73)
Nationalities, n (%)	
- Non-Qatari	640 (69.79)
- Qatari	277 (30.21)
CAD, n (%)	130 (14.18)
PAD, n (%)	36 (3.93)
COPD, n (%)	39 (4.25)
Heart failure, n (%)	63 (6.87)
Liver disease, n (%)	53 (5.79)
DM, n (%)	378 (41.22)
Hypertension, n (%)	360 (39.3)
Active cancer, n (%)	107 (11.67)
Hematology cancer, n (%)	24 (2.62)
NSAID, n (%)	142 (15.49)
ACEI/ARB, n (%)	181 (19.74)
Vancomycin, n (%)	100 (10.91)
Acyclovir, n (%)	20 (2.18)
Diuretics, n (%)	169 (18.43)
Pneumonia, n (%)	406 (44.27)
Endocarditis, n (%)	1 (0.11)
Febrile neutropenia, n (%)	24 (2.62)
Urinary tract, n (%)	96 (10.47)
Abdominal infection, n (%)	181 (19.74)
Musculoskeletal, n (%)	107 (11.67)
Septicemia, n (%)	183 (19.98)
Others, n (%)	131 (14.3)
AKI, n (%)	98 (10.7)
Baseline creatinine, mean (SD)	69.50 (17.75)
Creatinine after TAZ/PIPC initiation, mean (SD)	76.63 (43.93)
Duration of TAZ/PIPC therapy, mean (SD)	6.13 (4.17)
Duration of TAZ/PIPC until AKI, mean (SD)	4.46 (3.20)
Albumin, mean (SD)	27.38 (6.46)
Fasting blood glucose, mean (SD)	7.58 (3.53)
AKI duration, mean (SD)	10.93 (18.73)
Renal replacement therapy, n (%)	17 (1.9)
In-hospital mortality, n (%)	80 (8.72)

Table 2. Comparison between AKI group and non-AKI group in relation to demographic, clinical characterestics of patients involved in this study.

Characteristics	Total (N=917)	AKI Negative (N=819)	AKI Positive (N=98)	P-value
Age, mean (SD)	51.98 (18.97)	51.06 (18.67)	59.71 (19.79)	<0.001
Male, n (%)	635 (69.25)	573 (69.96)	62 (63.27)	0.174
Qatari, n (%)	277 (30.21)	242 (29.55)	35 (35.71)	0.209
BMI, mean (SD)	27.04 (6.73)	26.89 (6.62)	28.29 (7.45)	0.051
Baseline creatinine, mean (SD)	69.50 (17.75)	67.84 (17.20)	83.33 (16.29)	<0.001
Creatinine after TAZ/PIPC initiation	76.63 (43.93)	66.78 (21.42)	158.91 (81.93)	<0.001
Duration of TAZ/PIPC, mean (SD)	6.13 (4.17)	6.07 (4.24)	6.75 (3.53)	0.268
Albumin, mean (SD)	27.29 (6.99)	27.60 (6.98)	24.75 (6.59)	<0.001
Fasting blood glucose, mean (SD)	7.58 (3.53)	7.4 (3.37)	9.07 (4.38)	<0.001
Coronary artery disease (CAD), n (%)	130 (14.18)	103 (12.58)	27 (27.55)	<0.001
Peripheral artery disease (PAD), n (%)	36 (3.93)	31 (3.79)	5 (5.1)	0.526
COPD, n (%)	39 (4.25)	35 (4.27)	4 (4.08)	0.929
Heart failure, n (%)	63 (6.87)	41 (5.01)	22 (22.45)	<0.001
Liver disease, n (%)	53 (5.79)	43 (5.26)	10 (10.2)	0.047
Diabetes mellitus, n (%)	378 (41.22)	327 (39.93)	51 (52.04)	0.021
Hypertension, n (%)	360 (39.3)	302 (36.92)	58 (59.18)	<0.001
Active cancer, n (%)	107 (11.67)	92 (11.23)	15 (15.31)	0.235
Hematology cancer, n (%)	24 (2.62)	19 (2.32)	5 (5.1)	0.103
NSAID, n (%)	142 (15.49)	131 (16.0)	11 (11.22)	0.217
ACEI/ARB, n (%)	181 (19.74)	159 (19.41)	22 (22.45)	0.476
Vancomycin, n (%)	100 (10.91)	79 (9.65)	21 (21.43)	<0.001
Acyclovir, n (%)	20 (2.18)	19 (2.32)	1 (1.02)	0.405
Diuretics, n (%)	169 (18.43)	121 (14.77)	48 (48.98)	<0.001
Pneumonia, n (%)	406 (44.27)	348 (42.49)	58 (59.18)	0.002
Endocarditis, n (%)	1 (0.11)	1 (0.12)	0 (0)	0.729
Febrile neutropenia, n (%)	24 (2.62)	22 (2.69)	2 (2.04)	0.705
Urinary tract, n (%)	96 (10.47)	84 (10.26)	12 (12.24)	0.543
Abdominal infection, n (%)	181 (19.74)	174 (21.25)	7 (7.14)	0.001
Musculoskeletal, n (%)	107 (11.67)	98 (11.97)	9 (9.18)	0.418
Septicemia, n (%)	183 (19.98)	152 (18.58)	31 (31.63)	0.002
In-hospital mortality, n (%)	80 (8.72)	42 (5.13)	38 (38.78)	<0.001

significantly higher in the AKI group [38.78% versus 5.13% in the non-AKI group; $P<0.001$]. Table 2 summarizes the conditions associated with AKI in this study.

The Outcomes and the Independent Risk Factors for AKI

The in-hospital mortality was 80 (8.72%). **Table 3** describes the outcomes of the cohort of this study. After adjusting the relationship to include many variables, and by using conditional multiple logistic regression analysis, only advanced age (adjusted OR=0.96, 95% CI = 0.93-1.00, P= 0.03) and heart failure (adjusted OR=3.8, 95%CI=1.16-12.54, P=0.02) were found to be independent risk factors for AKI (**Table 4**).

Table 3. Outcomes of the cohort of this study.

Outcomes	N (%)
Creatinine after TAZ/PIPC initiation, mean (SD)	76.63 (43.93)
AKI, n (%)	98 (10.7)
AKI duration, mean (SD)	10.93 (18.73)
Renal replacement therapy, n (%)	17 (1.9)
In-hospital mortality, n (%)	80 (8.72)

DISCUSSION

TAZ / PIPC is one of the most commonly used antibiotics in our hospital. Its effectiveness is attributed to its ability to cover broad-spectrum gram-negative microorganisms and anaerobic agents. At the time of introduction to our hospital, it was an unrestricted antibiotic that allowed any physician to prescribe the antibiotic indefinitely.

Table 4. Results of multivariate analysis of predictors of AKI.

Variables	Adjusted OR	P value
Age	0.96 (0.93-1.00)	0.038
Baseline creatinine	0.98 (0.96-1.01)	0.214
Creatinine after TAZ/ PIPC initiation	1.03 (1.00-1.06)	0.079
Albumin	1.00 (0.94-1.06)	0.951
Fasting blood glucose	0.96 (0.86-1.07)	0.474
CAD	1.51 (0.51-4.48)	0.460
Heart failure	3.80 (1.16-12.45)	0.027
Liver disease	1.54 (0.40-5.89)	0.531
Diabetes mellitus	0.36 (0.12-1.08)	0.069
Hypertension	1.57 (0.49-4.98)	0.447
Vancomycin	0.47 (0.14-1.58)	0.219
Diuretics	0.63 (0.25-1.62)	0.342
Pneumonia	1.48 (0.62-3.52)	0.371
Abdominal infection	0.35 (0.09-1.35)	0.128
Septicemia	2.49 (0.94-6.59)	0.065
In-hospital mortality	1.56 (0.47-5.19)	0.467

However, because of its high prescription volume and rising expenses[1], a restriction decision has been made in the last three years till present, in an attempt to monitor and control the judicious use of this antibiotic. As part of a stewardship program in Hamad Medical Corporation (HMC), TAZ/PIPC was placed on a 48-hour restriction, therefore, any physician could order the antibiotic, but each order would be given a 48-hour stop date, after which it is subjected to a review by an infectious disease physician.

To our knowledge, this is the first study to report TAZ/PIPC-associated AKI among patients treated in Hamad General Hospital, Qatar. We think our results will support the efforts of the stewardship program designers to restrict the use of this antibiotic in HMC to avoid unwanted side effects such as AKI that results from the judicious use of this antibiotic.

Regardless of the characteristics of the population analyzed and the criteria used to diagnose AKI, TAZ / PIPC-associated AKI has been reported by several authors with various frequencies; the estimated frequency varies between 7.8 and 38.5% of cases.[3-9] In our study, the frequency of TAZ/PIPC-associated AKI was 10.7% of cases, which falls within the international range. TAZ/PIPC is often co-administered with vancomycin to cover methicillin-resistant Gram-positive organisms in various infections such as catheter-related bloodstream infections. It has recently been reported that patients receiving a combination of vancomycin and TAZ / PIPC had a relatively high AKI level compared to patients receiving vancomycin alone.[3,4,10-13] Although our study was not designed to compare between patients who used vancomycin in combination with TAZ/PIPC and patients who received TAZ/PIPC alone, the number of patients who received vancomycin in the AKI group was significantly higher than the patient in the non-AKI group [21 (21.43%) vs. 79 (9.65%); P<0.001], which is in keeping with the above studies. Based on this finding, patients receiving a combination of vancomycin and TAZ

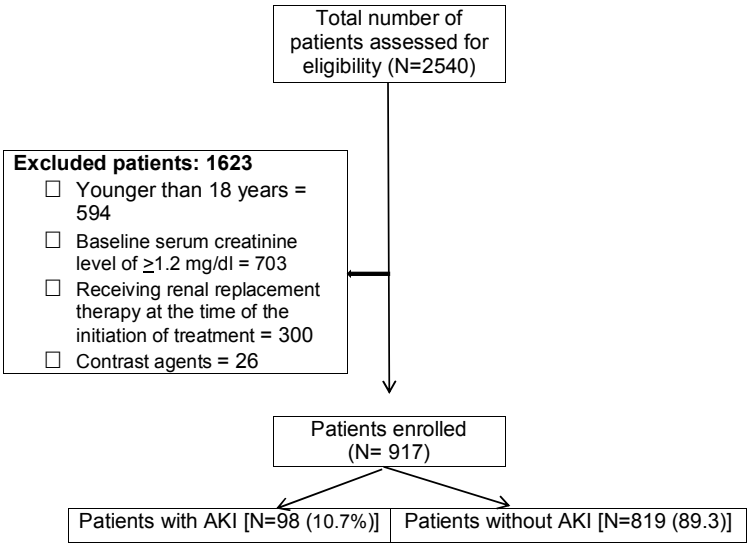

Figure 1. A flow chart of patients recruitment in this study

/ PIPC should, therefore, be closely monitored for the development of AKI and it would be better if they were switched to a less nephrotoxic regimen. Moreover, we found that the AKI group used more diuretics than the non-AKI group [48 (48.98%) vs. 121 (14.77%); P<0.001], which is contrary to a report by Rutter et al.[4] The exact mechanism of AKI in these patients is unclear. However, this finding indicates that we should use TAZ/PIPC cautiously in patients under diuretics.

Of note, the duration of TAZ/PIPC use was significantly longer in the AKI group than in the non-AKI group [7.44 (SD 6.09) vs. 6.04 (SD 4.24); P=0.004], which coincide with other reports in the literature.[14] Therefore, we support the stewardship program recommendation on the restriction of TAZ/PIPC, as this step will shorten the duration of exposure of the patients to this drug. Our study also showed a significant association between AKI and many variables such as low serum albumin, diabetes mellitus, coronary artery disease, liver disease, pneumonia, abdomen infection, sepsis and hypertension. In critically ill patients with sepsis, AKI is a recognized clinical entity; in one study,[15] it was found in 66% of patients admitted to the intensive care unit. In such a case, AKI may be a consequence of the sepsis itself or of therapeutic interventions that include drugs like vancomycin and TAZ/ PIP, or the dual effect of both. In the same context, Jensen et al. observed that in patients with sepsis-related renal dysfunction, exposure to TAZ/ PIP is associated with a lower rate of improvement in glomerular filtration rate (GFR) compared to other antibiotics and that the kidney function improves rapidly after stopping this medication.[16] Given this finding, let us conclude that patients with sepsis are more susceptible to AKI if they receive TAZ/ PIP. Further prospective RCTs are needed to confirm this observation. However, it is advisable to look for effective strategies to reduce nephrotoxicity in this group of patients. Suggested strategies include avoiding dehydration and co-administration of other nephrotoxic agents. Other actions include close monitoring of renal function, early and repeated reevaluations of empirical antibiotic therapy with appropriate alterations, and the use of alternatives to TAZ/PIP such as cefepime or an antipseudomonal carbapenem.[17] On the other hand, the reason for the significant association between AKI and hypertension in patients receiving TAZ/PIP is unclear, however, it could be attributed to the pre-existing hypertensive renal disease.

Interestingly, we only found advanced age and heart failure to be associated significantly with AKI in both bivariate and multivariate analyses. The association of advanced age and heart failure with AKI in patients receiving TAZ/ PIPC could be explained by the fact that heart failure and advanced age cause reduced renal blood flow[13,14] that may aggravate tubular injury related to TAZ/PIPC, by limiting oxygen and nutrient availability and facilitating oxidative stress. We, therefore, recommend caution when using TAZ/ PIPC in patients with advanced age and heart failure who should be closely monitored for the development of AKI. To our knowledge, this is the first clinical study to report heart failure as an independent risk factor for AKI associated with TAZ/PIPC administration.

A noteworthy finding of this study is that the in-hospital mortality was higher in AKI patients compared to non-AKI patients [38 (38.78%) vs. 24 (5.13%); p = 0.02], which is consistent with emerging evidence suggesting that there are higher in-hospital mortality rates with even smaller changes in serum creatinine level.[18] However, the impact of TIZ/PIP-associated AKI on mortality is unclear due to the lack of information and the paucity of studies.

Our study has several limitations. First, it was a retrospective study that did not allow us to study in detail many variables, such as the reason for the prolonged use of TAZ/ PIPC in some patients in our study over a period of up to 42 days. Moreover, we did not have detailed information about other medications used during the study period. Second, we have excluded patients under the age of 18 years. As a result, we missed the opportunity to estimate the prevalence of TAZ/ PIPC-induced AKI among different groups in our hospital. Third, we did not have the facilities to measure TAZ/ PIPC levels to assess whether patients with AKI had higher

TAZ/ PIPC blood levels or not. Fourth, This was a hospital-based study, despite the large sample size, therefore, the results may not be applicable to other hospitals.

CONCLUSION

We found that TAZ/PIPC was associated with AKI and that co-administration of TAZ/ PIPC with vancomycin or diuretics resulted in a high rate of AKI compared to patients receiving TAZ/PIPC alone. Advanced age and heart failure have been identified as independent risk factors for TAZ/PIPC-induced AKI that should be targeted to prevent AKI and improve patient outcomes. We, therefore, recommend baseline evaluation and continuous monitoring of renal function in high-risk patients receiving TAZ/ PIPC therapy.

CONFLICT OF INTEREST

There is no conflict of interest.

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