Current Concepts in the Diagnosis and Classification of Renal Dysfunction in Cirrhosis

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Abstract
Background: Renal dysfunction is one of the most common complications of cirrhosis with high morbidity and mortality.
Summary: In subjects with cirrhosis, renal dysfunction can present either as a direct consequence of cirrhosis (e.g. hepatorenal syndrome type I and type II) or secondary to etiologies other than cirrhosis (chronic kidney disease due to diabetic nephropathy, prerenal azotemia), or patients with cirrhosis may have renal dysfunction resulting directly from cirrhosis and an underlying chronic kidney disease.
Key Messages: Given the challenges in the differential diagnosis of renal dysfunction and insufficient accuracy of serum creatinine and creatinine-based glomerular filtration rate estimating equations in cirrhosis, there is an urgent need for more accurate biomarkers of renal dysfunction in this population.

Introduction

Renal dysfunction is one of the most common complications in cirrhosis with high morbidity and mortality [1–3]. The prevalence of all kidney-related disorders in cirrhosis (hepatorenal disorders) was reported as 20% [4]. There is an overwhelming burden of advanced kidney disease in patients with cirrhosis; based on Organ Procurement and Transplantation Network data as of January 18, 2013, more than 4,700 adult liver transplants were performed in 2012, of which 8% were simultaneous liver-kidney transplant [5]. The proportion of patients who underwent simultane-
Hepatorenal disorders commonly encountered in subjects with cirrhosis are either a direct consequence of the underlying cirrhosis affecting the kidneys (hepatorenal syndrome, HRS) [6, 7] or secondary to etiologies other than cirrhosis per se (e.g. prerenal azotemia due to gastrointestinal bleeding). In a conventional definition described by Salerno et al. [7], HRS type II is a functional renal disorder that is accompanied by a serum creatinine elevation above 1.5 mg/dl occurring in patients with cirrhosis and ascites in the absence of shock, nephrotoxic drugs and intrinsic kidney disease. On the other hand, HRS type I is a more rapidly progressing functional renal disorder in which serum creatinine doubles from the baseline level and increases over 2.5 mg/dl within 2 weeks [7]. Median survival probabilities were reported as 1 and 6.7 months in patients with cirrhosis with HRS type I and II, respectively [8].

Current drug treatments of HRS type I target reversing the vasodilatation in the splanchnic circulation and reversing the vasoconstriction in the renal vasculature with a restoration of impaired renal blood flow [9, 10]. They include vasopressin analogues (e.g. terlipressin; not FDA-approved), somatostatin analogues (e.g. octreotide), α-adrenergic receptor agonists (e.g. midodrine) along with albumin infusion [9, 10]. A meta-analysis that comprised 6 randomized-controlled trials of vasoconstrictor drugs with or without albumin showed that patients who received vasoconstrictor treatment with or without albumin for HRS were 18% less likely to die compared to controls who did not receive any intervention or had only albumin infusion [3]. A meta-analysis of 4 randomized-controlled studies showed that patients who were treated with terlipressin with or without albumin were 3.8 times more likely to reverse HRS and 2.0 times more likely to have an improved renal function compared to those who did not receive any intervention, or had only albumin infusion [3]. Despite these encouraging results, vasoconstrictor treatment with or without albumin was effective only in reducing mortality at 15 days without any significant effect at 1, 3 and 6 months [3]. In addition, vasoconstrictor treatment was effective in reversing HRS and improving renal function only in 46 and 48% of patients, respectively [3].

One of the major factors for insufficient effectiveness of vasoconstrictor treatment can be due to delays in administration of these drugs secondary to diagnostic challenges (e.g. differentiation of HRS from other causes of acute kidney injury, AKI; waiting for serum creatinine to reach 2.5 mg/dl according to currently used criteria defined by Salerno et al. [7]). Differentiation of the functional hepatorenal disorders (i.e. HRS) from hepatorenal disorders secondary to etiologies other than cirrhosis (e.g. prerenal azotemia, chronic kidney disease) still remain a challenging task for clinicians. Patients with cirrhosis may have underlying chronic kidney disease that may complicate accurate diagnosis of additional injury resulting directly from the cirrhosis (e.g. differentiation of HRS type II from diabetic nephropathy). The most important dilemma in the diagnosis of hepatorenal disorders is encountered in the acute setting. Most often, patients with cirrhosis may present not only with a single kidney disorder, but also with a combination of kidney disorders. For instance, a patient with decompensated cirrhosis with HRS type II can present with severe upper gastrointestinal bleeding and progress to HRS type I in the presence of sepsis or bacteremia, making differentiation of functional renal failure almost impossible from prerenal azotemia induced by bleeding. A similar dilemma that is encountered in the diagnosis of hepatorenal disorders exists in the classification of renal dysfunction in cirrhosis.

In this review, we discuss novel concepts introduced for the classification and diagnosis of renal dysfunction in cirrhosis. In addition, we propose a new classification system for renal dysfunction in cirrhosis.

Importance of Renal Blood Flow in Classification of Renal Dysfunction in Cirrhosis

Recently, a working party that comprised members of the Acute Dialysis Quality Initiative (ADQI) and International Ascites Club (IAC) proposed a new classification system for hepatorenal disorders in cirrhosis [11]. According to this classification, while HRS type I was categorized as a special form of AKI, HRS type II was not considered as a special form of chronic kidney disease [11]. There is an ongoing debate concerning the classification of HRS type II. Some experts oppose the consideration of HRS type II as a structural chronic kidney disease for insufficient effectiveness of vasoconstrictor treatment can be due to delays in administration of these drugs secondary to diagnostic challenges (e.g. differentiation of HRS from other causes of acute kidney injury, AKI; waiting for serum creatinine to reach 2.5 mg/dl according to currently used criteria defined by Salerno et al. [7]). Differentiation of the functional hepatorenal disorders (i.e. HRS) from hepatorenal disorders secondary to etiologies other than cirrhosis (e.g. prerenal azotemia, chronic kidney disease) still remain a challenging task for clinicians. Patients with cirrhosis may have underlying chronic kidney disease that may complicate accurate diagnosis of additional injury resulting directly from the cirrhosis (e.g. differentiation of HRS type II from diabetic nephropathy). The most important dilemma in the diagnosis of hepatorenal disorders is encountered in the acute setting. Most often, patients with cirrhosis may present not only with a single kidney disorder, but also with a combination of kidney disorders. For instance, a patient with decompensated cirrhosis with HRS type II can present with severe upper gastrointestinal bleeding and progress to HRS type I in the presence of sepsis or bacteremia, making differentiation of functional renal failure almost impossible from prerenal azotemia induced by bleeding. A similar dilemma that is encountered in the diagnosis of hepatorenal disorders exists in the classification of renal dysfunction in cirrhosis.

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Renal Dysfunction in Cirrhosis

Renal dysfunction originating directly from the underlying cirrhosis can range from mild to moderate reduction in renal blood flow to severe renal vasoconstriction, resulting in HRS. In patients with cirrhosis, either excessive or insufficient production of nitric oxide (NO) results in reduced renal blood flow [13–15]. Excessive endothelial NO production results in splanchnic vasodilation that reduces effective arterial blood volume [13–15]. In turn, the renin-angiotensin-aldosterone system, RAAS, is activated, resulting in renal vasoconstriction and reduced renal blood flow [13–15]. While the mechanism of reduced renal blood flow can be explained by excessive NO production, there is also insufficient NO production in the kidney, contributing to reduced renal blood flow [13–15]. Several investigators hypothesized that dimethylarginines including symmetric (SDMA) and asymmetric dimethylarginine (ADMA) play a key role in the NO insufficiency that leads to reduced renal blood flow [13–17].

NO generation occurs from L-arginine by NOS [18, 19]. In cirrhosis, NO synthesis is inhibited by increased ADMA levels [13, 18] reducing NO production and compromising renal blood flow [13–16]. In cirrhosis, the accumulation of ADMA levels occurs [13, 17, 20–25] because dimethylarginine dimethylaminohydrolase that hydrolyzes ADMA requires intact liver function [15]. In addition to elevated plasma ADMA levels in cirrhosis, plasma SDMA levels are also increased due to impaired hepatic and renal clearance [13, 21]. Therefore, SDMA competes with L-arginine for endothelial transport [21]. As mentioned above, L-arginine is a substrate for NOS; reduction in L-arginine levels further reduces NO production, thereby further reducing renal blood flow in cirrhosis [13–17].

The ratio of GFR to the renal plasma flow (RPF) represents the filtration fraction [26]. Subjects with compensated cirrhosis often have normal kidney function despite mild to moderate reduction in RPF [12]. In patients with cirrhosis, GFR is often maintained at normal or low/normal levels by a compensatory increase in filtration fraction. Increasing filtration fraction by angiotensin II-induced efferent arteriolar vasoconstriction is a well-known adaptive mechanism whereby the kidneys maintain GFR in conditions of diminished effective arterial blood volume [26]. Since increased filtration fraction by angiotensin II-induced efferent arteriolar vasoconstriction may mask the effect of reduced RPF on GFR, it is unknown at which stage of cirrhosis or by which mechanism(s) a reduction in renal plasma flow occurs in cirrhosis.

In the 1970’s, an elegant study by Kew et al. [12] suggested that reduced RPF can occur even in compensated cirrhosis. Moreover, they showed that in subjects with cirrhosis severe impairment in renal cortical blood flow was a landmark feature of renal dysfunction in cirrhosis that resulted in substantial reduction in GFR [12]. Rivolta et al. [27], who assessed renal blood flow by measuring renal resistive indices using Doppler ultrasonography, confirmed this finding and concluded that the difference between renal/interlobar and cortical resistive indices diminished over the progression in the degree of ascites. Several investigators suggested that there is a progressive reduction in kidney function associated with the severity of portal hypertension in subjects with cirrhosis [27–31]. In the 1950’s, Leslie et al. [31] showed that in subjects with cirrhosis the degree of ascites was closely associated with the degree of impairment in GFR and RPF. They found that in subjects with cirrhosis who had no ascites, the mean filtration fraction was increased, whilst mean GFR and RPF were within normal range compared to normal reference values [31]. Conversely, in subjects with cirrhosis and ascites responsive to treatment, mean filtration fraction was within the normal range, but the mean GFR and RPF were decreased, and in subjects with cirrhosis and ascites unresponsive to treatment, mean GFR and RPF were further reduced [31]. As GFR and RPF were not adjusted for body surface area, it is unclear if RPF or GFR would be even lower than reported [31]. Wong et al. [32] reported reduced mean GFR, RPF (adjusted for body surface area) and filtration fraction in subjects with cirrhosis and diuretic-refractory ascites. Similarly, our recent study showed a gradual decline in measured GFR over the progression in the degree of ascites in subjects with cirrhosis [30]. Rivolta et al. [27] showed significantly increased renal resistive indices in subjects with cirrhosis and refractory ascites compared to those without ascites or with diuretic-sensitive ascites. A study by Platt et al.
[33] revealed that a renal resistive index equal or greater than 0.70 was an independent predictor of HRS in subjects with cirrhosis whose serum creatinine was equal to or lower than 1.5 mg/dl. Therefore, based on the results of these studies, we suggest that HRS should not be defined by a stringent serum creatinine [7], but rather it should be viewed as the most severe form of acute (HRS type I) or chronic renal vasoconstriction (HRS type II) in cirrhosis.

A New Classification for Renal Dysfunction in Cirrhosis

We propose a new classification of renal dysfunction in cirrhosis (fig. 1). This classification system differs in several aspects from the classification that was previously suggested by the ADQI-IAC Working Party [11]: (1) It considers abnormalities of GFR in cirrhosis in combination with RPF and classifies renal dysfunction in four different severity stages, including stage 0, stage 1, stage 2, stage 3 and stage 4; (2) it is a dynamic classification system that allows patients with cirrhosis to move from milder stages to more advanced stages or from advanced stages to normal or milder stages, and (3) most importantly, we define a new patient population with cirrhosis who have a reduced RPF with normal or low/normal GFR. We propose to identify this population as ‘Pre-HRS’. Hypothetically, subjects with cirrhosis with no clinical evidence of fluid overload can be categorized under stage 0 where GFR and RPF are normal (fig. 1). In subjects with cirrhosis and baseline chronic kidney disease, GFR is reduced at baseline. With the progression of cirrhosis, some fluid accumulation can occur. This can be in the form of pedal edema and/or minimal ascites and/or diuretic-sensitive ascites where RPF is expected to decrease with a GFR maintained at normal/low normal level by increased filtration fraction (stage 1). The recognition and identification of patients with cirrhosis and ‘Pre-HRS’ (stage 1) is particularly important from the early intervention and prevention standpoint because these patients are susceptible to progress to HRS type I or II rapidly following spontaneous bacterial peritonitis, sepsis, aggressive diuresis, frequent or large volume paracenteses or administration of medications that can impair the adaptive response of kidneys to RAAS activation (e.g. nonsteroidal anti-inflammatory drugs, angiotensin II-receptor blockers, angiotensin-converting enzyme inhibitors). In stage 2, a significant reduction in GFR and RPF should be expected, particularly in subjects with cirrhosis and diuretic-refractory ascites. Impairment in RPF can be due to etiologies other than HRS type I or II (e.g. hypovolemia), and this needs to be taken into account in the differential diagnosis of both stages 1 and 2. In stages 3 and 4, either due to severity or prolonged duration of impairment in RPF and GFR, patients can progress to ischemic acute tubular necrosis with partial or complete recovery, or without recovery.

As laborious and time-consuming GFR and RPF measurements as well as expensive renal Doppler ultrasonography cannot be easily applied in clinical practice, we believe that the discovery of novel noninvasive biomarkers of reduced RPF and more accurate filtration markers than serum creatinine can easily identify subjects with cirrhosis with mild to severe reduction in RPF and GFR. This could result in earlier administration of vasostrictors and albumin, preventing progression to ischemic acute tubular necrosis.

New Concepts in the Diagnosis of AKI in Cirrhosis

In a joint conference, the ADQI-IAC Working Party proposed HRS to be a form of AKI in cirrhosis [11]. As AKI is a nonsteady state of renal dysfunction with associated increased urinary creatinine secretion, the GFR measurement, GFR estimation based on serum creatinine- or creatinine-cystatin C equations, 24-hour creatinine clearance or its estimation by the Cockcroft-Gault equation will not be accurate [34]. On the other hand, there is still no accurate and precise biomarker of HRS to be used in clinical practice. Lluch et al. [13] suggested that SDMA might be a potential marker of HRS. They also showed that in addition to SDMA, ADMA and NO were elevated in HRS [13]. The challenging issue here is that the accumulation of SDMA and ADMA can also occur in nonrenal and renal conditions other than HRS [35–37], and the predictive accuracy of these biomarkers in the differentiation of HRS from prerenal azotemia or HRS progressed to acute tubular necrosis compared to existing criteria is currently unknown.

In 2007, the Acute Kidney Injury Network (AKIN) Group reported a diagnosis and classification criteria for acute renal failure/AKI [38]. According to AKIN criteria, the diagnosis of AKI is based on an increase in serum creatinine of greater than or equal to 0.3 mg/dl from
Fig. 1. Proposed classification of renal dysfunction in cirrhosis based on renal plasma flow and GFR.

*Spot urine protein to creatinine ratio should be checked to ascertain the absence of a glomerular disease.
baseline or an increase in serum creatinine of greater than or equal to 50% (1.5-fold) from baseline or the presence of oliguria (urine output less than 0.5 ml/kg/h) for greater than 6 within 48 h [38]. The ADQI-IAC Working Party adopted AKIN criteria to diagnose AKI in patients with cirrhosis [11] and suggested that AKIN criteria should be used in cirrhosis for the diagnosis of AKI regardless of the presence of HRS type I [11]. The Working Party also agreed that current diagnostic criteria for HRS type I had limitations for early diagnosis and timely treatment of patients with cirrhosis and AKI [7, 11]. The ADQI-IAC Working Group agreed that the AKIN criterion of oliguria may not be adopted as subjects with cirrhosis with refractory ascites can have oliguria without developing AKI [11].

Recently, the AKIN criteria to diagnose AKI in cirrhosis have been validated by several investigators [39–41]. de Carvalho et al. [40] conducted a study including 198 admissions of cirrhosis. The authors did not measure baseline serum creatinine; instead they measured two serum creatinine levels taken 48 h apart during the patients’ hospitalization to determine the presence of AKI [40]. The multivariate logistic analysis showed that controlling for Child score, encephalopathy and infection, patients with AKI were 3.3 times more likely to die compared to those without AKI [40].

Similar findings were shown in an elegant inpatient study [39]. Belcher et al. [39] conducted a multicenter observational cohort study to determine the association between AKI diagnosed based on AKIN criteria and mortality among 192 inpatients with cirrhosis. The authors showed that progression of AKI stages defined according to AKIN criteria was an independent predictor of inpatient mortality [39]. Their multiple logistic regression analysis showed that controlling for demographics, renal function, in-hospital events, cirrhosis variables, patients who had progression in AKI stages (progressors) were 3.8 times more likely to die during the index hospitalization compared to nonprogressors [39].

To examine the prevalence and outcomes of AKI, Tsien et al. [41] conducted a prospective study that included 90 outpatients with cirrhosis and ascites. They showed that AKI occurred in 49 out of 90 patients with cirrhosis and ascites during a mean follow-up of 14 months with a total of 82 episodes of AKI [41]. The major precipitating factors for AKI included excessive diuretic use, large volume paracenteses, gastrointestinal bleeding (variceal and nonvariceal), infections and intravenous contrast administration [41]. In terms of patient outcomes, the patients with AKI had significantly lower survival probability compared to those without AKI [41].

Assessment of Nonacute Renal Dysfunction in Subjects with Cirrhosis

In both acute renal dysfunction and chronic renal dysfunction in cirrhosis, serum creatinine is not an accurate marker of kidney function. The synthesis of creatine that is a precursor of creatinine is impaired in cirrhosis [42, 43]. Sarcopenia, malnutrition, protein-restricted diet and increased tubular secretion further lower creatinine levels and reduce the accuracy of serum creatinine and 24-hour creatinine clearance in cirrhosis to estimate GFR [42–46]. Several studies showed that creatinine-based GFR-estimating equations overestimated true kidney function in cirrhosis and lacked sufficient accuracy when compared to measured GFR [47–49]. Moreover, the use of serum creatinine in the calculation of Model for End-Stage Liver Disease (MELD) scores can result in gender disparity on the liver transplant waiting list by lowering women’s MELD scores as women have significantly lower muscle mass and therefore significantly reduced serum creatinine levels compared to men [45]. We showed that women with cirrhosis on the US liver transplant waiting list had a significantly higher cumulative incidence of death within 3 years of listing compared to men [45]. In a subsequent study, we showed that there was also gender disparity among patients with cirrhosis and renal dysfunction not on dialysis on the liver transplant waiting list for undergoing simultaneous liver–kidney transplantation versus liver transplantation alone [50].

One alternative to using serum creatinine in estimating the GFR in cirrhosis would be to measure GFR in place of 24-hour creatinine clearance, creatinine clearance-estimating equation (the Cockcroft-Gault equation) or creatinine-based estimating GFR equations. Although measuring GFR is a gold standard method to assess kidney function, it is laborious, expensive, time-consuming and not practical in clinical practice. In addition, some GFR measurement methods expose the patients to radiation [46].
The second alternative to creatinine in estimating kidney function in cirrhosis is cystatin C-based equations. The use of cystatin C has several advantages over the use of serum creatinine in cirrhosis. Cystatin C is not dependent on an intact hepatic function and subjects with cirrhosis do not have increased tubular secretion of cystatin C [46]. Cystatin C levels are not affected or are less affected than creatinine by muscle mass, gender, race, protein-restricted diet and other factors [51, 52]. All of these features make cystatin C an attractive endogenous GFR marker in cirrhosis.

Several investigators investigated the accuracy of cystatin C in estimating kidney function in cirrhosis [53–57]. Although these studies suggested that cystatin C was a more accurate GFR marker than creatinine, they had limitations [53–57]. GFR was not measured by gold standard methods [53–56], it is unknown whether creatinine was calibrated by isotope dilution mass spectrometry (IDMS) as recommended by the National Kidney Disease Education Program [53–58], the accuracy of cystatin C in different severity stages and etiologies of cirrhosis was not studied [53] and intra-individual variability of serum cystatin C was not assessed and compared to that of serum creatinine [53–57]. Additionally, in subjects with cirrhosis and hyperbilirubinemia, serum creatinine measurement errors might have occurred with the use of the Jaffé method [53, 54, 56, 57, 59].

Poge et al. [60] compared the accuracy of cystatin C-based GFR-estimating equations developed by Hoek et al. [61] and Larsson et al. [62]. The results showed that cystatin C-based GFR-estimating equations were more precise and correlated better with measured GFR than creatinine-based equations [60].

The first combined creatinine-cystatin C-based equation was developed by Stevens et al. [51]. The authors showed that the creatinine-cystatin C-based GFR-estimating equation was more accurate in estimating measured GFR in subjects with CKD compared to an equation based solely on cystatin C [51]. Recently, the same group developed a creatinine-cystatin C equation [63]. This new equation, called ‘Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C equation (2012)’ was found to be more accurate than conventional creatinine-based equations in non-cirrhotic populations [63]. We evaluated the performance of the CKD-EPI creatinine-cystatin C equation in subjects with cirrhosis and compared its performance in estimating GFR to that of creatinine clearance, the Cockcroft-Gault equation, creatinine, cystatin C, and both creatinine and cystatin C-based equations [30]. Our results showed that the CKD-EPI cystatin C-creatinine equation was the most accurate GFR-estimating equation compared to conventional creatinine- or cystatin C-based equations [30]. However, its accuracy was worse in subjects with cirrhosis when compared to the accuracy that was reported in subjects without cirrhosis [30].

In summary, it is noteworthy that none of the creatinine-based, cystatin C-based or combined creatinine-cystatin C-based GFR-estimating equations were developed to estimate GFR in patients with cirrhosis incorporating their demographic, laboratory and clinical characteristics. Most of these equations were specifically developed to estimate GFR in patients with chronic kidney disease and, therefore, their superior performance in estimating GFR in noncirrhotic populations may not apply to populations with cirrhosis.

Conclusions

**Classification of Renal Dysfunction in Cirrhosis**

In this review, we propose a new dynamic classification system for renal dysfunction in cirrhosis. We also propose recognition of a new group of patients with cirrhosis, defined as ‘pre-HRS’, to identify renal dysfunction at an earlier stage that is likely to be more amenable to treatment and prevention.

**Diagnosis of Acute Renal Dysfunction in Cirrhosis**

Based on recent studies, the AKIN criteria appeared to be a strong predictor of mortality in subjects with cirrhosis and AKI [39–41]. However, there are still no accurate biomarkers that will differentiate HRS type I from other kidney disorders with similar presentation (e.g. acute tubular necrosis) or biomarkers that will diagnose HRS even in the presence of other kidney disorders (e.g. chronic kidney disease). Belcher et al. [39] suggested that clinical trials should be conducted to test the efficacy of somatostatin (octreotide) and vasopressin analogues (terlipressin) in improving survival when HRS is diagnosed at an earlier stage using AKIN criteria rather than waiting until the serum creatinine increases to 2.5 mg/dl based on IAC [7] criteria. In patients with cirrhosis presenting with an episode of AKI, it would also be interesting to determine whether the increase of

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cystatin C from baseline would be an even more accurate predictor of mortality compared to the increase in serum creatinine.

Diagnosis of Nonacute Renal Dysfunction in Cirrhosis

Several studies showed that creatinine-based equations (e.g., 24-hour creatinine clearance, Cockcroft-Gault equation, Modification of Diet in Renal Disease equation) overestimated true GFR in cirrhosis [47–49]. In this setting, the accuracy of cystatin C as well as cystatin C-based GFR-estimating equations are superior to that of creatinine in estimating kidney function in cirrhosis [30]. The CKD-EPI cystatin C-creatinine equation was shown to be the most accurate GFR-estimating equation compared to conventional creatinine- or cystatin C-based equations in cirrhosis [30]. However, its accuracy was worse in subjects with cirrhosis when compared to the accuracy that was reported in subjects without cirrhosis [30]. We believe that novel biomarkers of GFR and renal blood flow in cirrhosis are needed and will likely improve accuracy in determining renal dysfunction in this special population.

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Disclosure Statement

None of the authors have conflicts of interest associated with the manuscript.

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