Hepatorenal Syndrome

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Abstract
Hepatorenal syndrome (HRS) is a serious event during the course of decompensated cirrhosis. Although the most characteristic feature of the syndrome is a functional renal failure due to intense renal vasoconstriction, it is a more generalized process affecting the heart, brain and splanchnic organs. There are two types of HRS. Type 1 HRS is characterized by a rapidly progressive impairment of the circulatory and renal functions associated with a very poor prognosis (median survival rate lower than 2 weeks). Type 2 HRS is characterized by a steady impairment of the circulatory and renal functions with a median survival of 6 months. The pathogenesis of HRS is a deterioration of the effective arterial blood volume due to splanchnic arterial vasodilation and a reduction in venous return and cardiac output. It is therefore not surprising that the syndrome can be reversed by the simultaneous administration of intravenous albumin and arterial vasoconstrictors. Intrarenal mechanisms are important as well and require prolonged improvement of the circulatory function to be deactivated. Long-term administration of intravenous albumin and vasoconstrictors or correction of portal hypertension with a transjugular intrahepatic portacaval shunt are effective treatments of HRS, and many serve as a bridge to liver transplantation, the treatment of choice in these patients.

Introduction
Hepatorenal syndrome (HRS) is a complication of patients with severe liver disease and portal hypertension characterized by renal vasoconstriction, intense reduction of glomerular filtration rate (GFR), and water and sodium retention [1, 2]. Systemic vascular resistance (SVR) is significantly reduced, which in turn determines arterial hypotension. This syndrome occurs late in cirrhosis when the circulatory disturbances are intense, although sometimes, it may also occur in the setting of acute liver failure. Patients with ascites and dilutional hyponatremia are a group specially susceptible to present HRS. The occurrence of this syndrome may be part of the natural history of the liver disease or precipitated by factors that induce renal hypoperfusion. HRS is the cirrhosis complication with the worst prognosis and reduced life expectancy. The lack of a diagnostic marker to this condition is related to its functional nature [2–4]. Thus, in such cases, it is most important to exclude other causes of renal insufficiency in order to establish a firm diagnosis of HRS [5]. The aim of this chapter is to discuss the advances in the therapy of patients with HRS.
**Definition**

HRS is a clinical condition that usually occurs in patients with advanced liver disease and portal hypertension that is characterized by a combination of disturbances in circulatory and kidney function [6]. The major abnormality in the systemic circulation is markedly reduced total SVR, which leads to a low arterial pressure. Kidney function is markedly impaired because of a severe reduction of renal blood flow. The reduction in renal blood flow is pathogenically related to the impairment in the systemic circulatory function. HRS occurs predominantly in the setting of cirrhosis, but it may also develop in other types of severe chronic liver diseases, such as alcoholic hepatitis, or in acute liver failure [7, 8]. Because of its functional nature and lack of structural changes in the kidneys HRS is, theoretically, reversible if the mechanisms leading to the active renal vasoconstriction are corrected.

**Pathogenesis**

The pathophysiologic hallmark of HRS is renal vasoconstriction. The kidneys are structurally intact [9–13]. The mechanism of this vasoconstriction is poorly understood and possibly multifactorial, involving increased vasoconstrictor and reduced vasodilator factors that act on the renal circulation. The most accepted theory on the pathogenesis of HRS (Arterial Vasodilation Theory) proposes that renal hypoperfusion represents the extreme manifestation of an underfilling of the arterial circulation secondary to a marked vasodilatation of the splanchnic area (fig. 1) [14]. This arterial underfilling would result in a progressive baroreceptor-mediated activation of vasoconstrictor systems (i.e., renin-angiotensin and sympathetic nervous systems) that would cause vasoconstriction not only in the renal circulation but also in other vascular beds (lower and upper extremities). The splanchnic area would escape to the effect of vasoconstrictors and a marked vasodilation would persist, probably because of the existence of very potent local vasodilator stimuli. In early phases following the development of ascites, renal perfusion would be maintained within normal or near-normal levels despite the overactivity of vasoconstrictor systems by an increased synthesis/activity of renal vasodilator factors. The development of renal hypoperfusion leading to HRS would occur either as a result of a maximal activation of vasoconstrictor systems that could not be counteracted by vasodilator factors, decreased activity of vasodilator factors, and/or increased production of intrarenal vasoconstrictor factors. An alternative theory proposes that renal vasoconstriction is the result of a direct relationship between the liver and the kidney, without any relationship with disturbances in systemic hemodynamics. The link between the liver and the kidney would be either a liver vasodilator factor, the synthesis of which would be reduced as a consequence of liver failure, or a hepatorenal reflex causing renal vasoconstriction.

Recently, a new concept has been introduced as contributing factor in the development of HRS. In this sense it has been hypothesized that if circulatory dysfunction in cirrhosis was solely due to the progression of splanchnic arterial vasodilation and the hyperdynamic circulation, a compensatory mechanism of this disorder, cardiac output, should increase with the progression of the disease as it occurs with other homeostatic mechanism of effective arterial blood volume, such as the overactivity of the renin-angiotensin and sympathetic nervous system. However, this is not the case. Despite the progressive increase in the plasma levels of renin and norepinephrine during the course of cirrhosis, indicating an accentuation of arterial vasodilation, cardiac output is similar in patients with compensated cirrhosis, nonazotemic cirrhotic patients with ascites and normal or increased plasma levels of renin and norepinephrine and patients with type 2 HRS. The heart rate also does not increase despite the progressive stimulation of the sympathetic nervous system. This feature suggests that circulatory dysfunction in cirrhosis is related not only to a progression of arterial vasodilation but also to an inability of the heart to in-
crease the cardiac output in response to a decrease in cardiac preload (fig. 2). The recent demonstration in nonazotemic patients with cirrhosis and spontaneous bacterial peritonitis that the development of type 1 HRS occurs in the setting of a significant decrease in cardiac output further supports that cardiac dysfunction is an important event in the pathogenesis of the impairment in circulatory and renal function in decompensated cirrhosis [15].

**Diagnosis**

HRS is the last clinical spectrum of abnormalities of renal function in patients with cirrhosis and ascites. HRS may occur in two different clinical patterns [6].

Type 1 HRS is characterized by rapid and progressive impairment of renal function as defined by a 100% increase of the initial serum creatinine to a level greater than 2.5 mg/dl or a 50% reduction of the initial 24-hour creatinine clearance to a level lower than 20 ml/min in less than 2 weeks. In some patients, this type of HRS develops spontaneously without any identifiable precipitating factor, while in others it occurs in close chronological relationship with some complicating event, particularly after the resolution of spontaneous bacterial peritonitis.

Type 2 HRS is characterized by a less severe and non-progressive reduction of glomerular filtration rate (at least in the short term); the main clinical consequence of this type of HRS is refractory ascites.

Because of the lack of specific diagnostic tests, the diagnosis of HRS is currently made according to several criteria, as proposed by the International Ascites Club, which are based on demonstration of a marked reduction in GFR (serum creatinine >1.5 mg/dl in the absence of diuretic therapy) and the exclusion of other causes of renal failure that may occur in patients with cirrhosis [6] (table 1).

For many years, no effective therapy existed for patients with HRS, except for liver transplantation. Recently, several effective new interventions have been introduced.

**Treatment of HRS**

**Management of Type 1**

Patients with suspected type 1 HRS should be managed as inpatients for diagnosis and treatment. Vital signs, blood chemistry, and urine output should be closely monitored. Because most patients have dilutional hyponatremia (serum sodium below 130 mmol/l), total flu-
Table 1. Diagnostic criteria of HRS – major and additional criteria

**Major criteria**
1. Low glomerular filtration rate, as indicated by serum creatinine greater than 1.5 mg/dl or 24-hour creatinine clearance lower than 40 ml/min
2. Absence of shock, ongoing bacterial infection, fluid losses and current treatment with nephrotoxic drugs
3. No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less or increase in creatinine clearance to 40 ml/min or more) following diuretic withdrawal, and expansion of plasma volume with 1.5 liters of a plasma expander
4. Proteinuria lower than 500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

**Additional criteria**
1. Urine volume lower than 500 ml/day
2. Urine sodium lower than 10 mmol/l
3. Urine osmolality greater than plasma osmolality
4. Urine red blood cells less than 50 per high-power field
5. Serum sodium concentration lower than 130 mmol/l

All major criteria must be present for the diagnosis of hepatorenal syndrome. Additional criteria are not necessary for the diagnosis, but provide supportive evidence.

id intake (both oral and intravenous fluids) should be restricted to avoid a positive fluid balance, which would lead to a further reduction in serum sodium concentration. In most cases, total fluid intake should be kept around 1,000 ml daily. In patients with severe oligoanuria, more severe fluid restriction (500–1,000 ml daily) may be needed to prevent a positive fluid balance and a progressive decline in serum sodium concentration. However, such a low input can be difficult to achieve because the administration of fluids cannot be reduced to such an extent in some patients and restriction is poorly tolerated by conscious patients. The administration of saline solutions can greatly increase ascites and edema because of the presence of severe renal sodium retention and therefore is not recommended. For this reason and because of the absence of severe metabolic acidosis in most patients, the routine administration of sodium bicarbonate is not advisable either. Potassium-sparing diuretics should be withheld because of the risk of inducing severe hyperkalemia. Early identification of infection and treatment with broad-spectrum antibiotics are fundamental, since severe infections are common and contribute to death in these patients. The efficacy of antibiotic prophylaxis for the prevention of infections in patients with HRS has not been assessed.

**Vasoconstrictors**
A number of nonrandomized studies published in the late 1990s and early 2000s have shown that the administration of vasoconstrictor drugs to patients with cirrhosis and HRS causes a marked improvement in renal function in a large proportion of patients [16–23]. The rationale for the use of vasoconstrictors in patients with HRS is to improve effective arterial blood volume by causing a vasoconstriction of the extremely dilated arterial splanchnic vascular bed. The improvement in the arterial circulatory function leads to a suppression in the activity of vasoconstrictor systems and a subsequent increase in renal perfusion and GFR [16].

Two types of drugs have been reported to be effective in HRS: vasopressin analogues (ornipressin and terlipressin) and α-adrenergic agonists (noradrenaline and midodrine), which act on V1 vasopressin receptors and α1-adrenergic receptors, respectively, present in vascular smooth muscle cells. In most studies, both drugs have been given in combination with intravenous albumin to further improve the arterial underfilling. A summary of the results obtained in published studies is shown in table 2. Currently, terlipressin is the vasoconstrictor drug more frequently used in HRS [19, 21, 22, 24, 25]. Ornipressin is also effective, but its use is not recommended because of the development of severe ischemic complications in up to one third of patients [16, 18]. Because there are no randomized studies investigating the efficacy and safety of terlipressin in patients with HRS, the existing information should be taken with caution (table 3).

Catecholamines are also effective for the treatment of HRS. Angeli et al. [17] used oral midodrine, an α-adrenergic agonist, intravenous albumin, and subcutaneous octreotide (to suppress glucagon) in 5 patients with type 1 HRS. Midodrine dosage (7.5–12.5 mg every 8 h) was adjusted to increase mean arterial pressure of 15 mm Hg or more. Patients received treatment for at least 20 days in hospital and continued treatment at home. In all cases, there was a marked improvement in renal perfusion, GFR and suppression of renin, aldosterone, norepinephrine and ADH to normal or near normal levels. Two patients were transplanted 20 and 64 days after inclusion while on therapy. One patient, who was not a candidate for liver transplantation, was alive without treatment 472 days after discharge from hospital. The remaining two died 29 and 75 days after treatment.
Duvoux et al. [20] treated 12 patients with type 1 HRS with intravenous albumin and noradrenaline (0.5–3.0 mg/h) for a minimum of 5 days. Reversal of HRS was observed in 10 patients in association with an increase in mean arterial pressure and a marked reduction in renin and aldosterone. There was an episode of reversible myocardial hypokinesia. Three patients were transplanted and 4 other cases had prolonged survival (over 6 months).

Recently, Wong et al. [23] studied 14 patients with cirrhosis and type 1 HRS; patients were treated with a combination of midodrine, octreotide, and albumin, followed by insertion of TIPS in selected patients, those with relatively preserved liver function (INR <2, bilirubin <5 mg/dl, and Child-Turcotte-Pugh score <12). The main finding of this study was that the insertion of TIPS in selected patients, following their response to vasoconstrictors, induced a normalization of renal function with the gradual elimination of ascites. Although the low number of evaluated patients and lack of randomization limit the relevance of the study to some extent, the information provided is of interest from both a pathogenic and a clinical perspective.

The improvement of renal function prior to transplantation is very important. A recent study by Restuccia et al. [26] analyzed the impact of treatment of HRS before liver transplantation on outcome after transplantation. The 3-year survival probability was similar in patients treated with vasopressin analogues before liver transplantation and contemporary patients transplanted without HRS (HRS 100 vs. 83% non-HRS, p = 0.15). No significant differences were found between the two groups with respect to the incidence of renal failure after liver transplantation (22 vs. 30%), severe infections (22 vs. 33%), acute rejection (33 vs. 41%), days in intensive care unit (6 ± 1 vs. 8 ± 1), days in hospital (27 ± 4 vs. 31 ± 4), and transfusion requirements (11 ± 3 vs. 10 ± 2 units). These results suggest that HRS should be treated before liver transplantation.

Transjugular Intrahepatic Portosystemic Shunts

Since portal hypertension is the triggering event leading to circulatory dysfunction in cirrhosis, the decrease of portal pressure is a rational approach for the treatment of HRS. There are several case reports showing reversal of HRS following surgical portacaval shunts. However, the applicability of major surgical procedures in patients with HRS is small, because of the extremely high mortality of these procedures in high-risk patients. The development of transjugular intrahepatic portosystemic shunts (TIPS) has reintroduced the idea of treating HRS by portacaval shunts. TIPS consists of the insertion of an intrahepatic stent between the portal and the hepatic veins using a transjugular approach and its main effect is to achieve a reduction in portal pressure by a nonsurgical method [27]. Two noncontrolled trials have been published describing the effect of TIPS on patients with type 1 HRS [28–30]. Altogether, renal function improved in some patients 1–4 weeks after TIPS placement. This improvement correlated with a decreased activity of the vasocon-
strictor systems, mainly the renin-angiotensin system, and, to a lesser extent, the sympathetic nervous system [30]. De novo hepatic encephalopathy or worsening of previous hepatic encephalopathy occurred in one-third of patients, but it could be controlled with lactulose in more than half. Median survival after TIPS in patients with type 1 HRS ranged between 2 and 4 months [29, 30]. As with vasoconstrictor drugs, it is likely, but not proved, that the improved renal function results in increased survival [28]. It should be pointed out that the information currently available on the use of TIPS in type 1 HRS has been obtained in a very selected population of patients and may not be applicable to the whole population of patients with type 1 HRS. In fact, TIPS is considered contraindicated in patients with severe liver failure (high serum bilirubin levels and/or a Child-Pugh score >12) or severe hepatic encephalopathy because of the risk of inducing irreversible liver failure or chronic disabling hepatic encephalopathy. No studies have been reported comparing TIPS and vasoconstrictors in type 1 HRS. Currently, vasoconstrictors appear to be the treatment of choice in type 1 HRS because of an apparent similar efficacy, wider availability, greater applicability, and lower costs compared with TIPS.

Liver Transplantation
Liver transplantation is the best treatment for suitable candidates with HRS because it offers a cure to the diseased liver and the HRS. However, a significant proportion of patients die before transplantation can be done because of their extremely short survival rate. Therefore, liver transplantation should be indicated before the development of HRS. The presence of HRS is associated with increased morbidity and early mortality after transplantation. Patients with ascites who are more likely to develop HRS are those with very reduced urine sodium (<10 mEq/l), dilutional hyponatremia, arterial hypotension, and marked activation of the renin-angiotensin and sympathetic nervous systems [31]. Consequently, patients with these signs should be evaluated for liver transplantation. The most common contraindications for transplantation in HRS are advanced age, active alcoholism, and infection. The main problem in performing the liver transplantation for type 1 HRS is that many patients die before transplantation, possibly because of the short survival expectancy and long waiting times in most transplant centers. Assigning to these patients a high priority for transplantation can solve the issue. The system allocation has been changed in the United States, and livers are now al-

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**Table 3.** Currently known information about terlipressin and topics for future research

<table>
<thead>
<tr>
<th>Available information</th>
<th>Areas for further research</th>
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<tbody>
<tr>
<td>The administration of terlipressin (0.5–2 mg/4–6 h i.v.) induce a complete renal response, defined by a reduction of serum creatinine from pretreatment values to a level below 1.5 mg/dl, in 50–75% of patients treated</td>
<td>The dose and frequency of terlipressin with the best efficacy/safety ratio are unknown</td>
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<tr>
<td>In most studies, treatment with terlipressin has been maintained until serum creatinine decreased below 1.5 mg/dl (responder patients) or for a maximum of 15 days</td>
<td>It is unknown whether the continued administration of the drug after the end-point of 1.5 mg/dl of serum creatinine has been reached may cause a further beneficial effect on renal function</td>
</tr>
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<td>In responder patients, the improvement in urine volume tends to occur immediately after the first doses of terlipressin (within 12–24 h), while that of glomerular filtration rate usually occurs slowly over several days</td>
<td>The possible beneficial effect of terlipressin on survival of patients with HRS has not been proved yet due to the lack of comparative studies including a control group of nontreated patients</td>
</tr>
<tr>
<td>L.v. albumin has been given at variable doses for the duration of therapy with terlipressin</td>
<td>The suggestion that i.v. albumin improves the beneficial effects of terlipressin on renal function remains to be proven in a prospective, randomized, comparative study</td>
</tr>
<tr>
<td>Recurrence of HRS after treatment withdrawal is uncommon (approximately 15% of patients); treatment of recurrence is usually effective</td>
<td>The efficacy of vasoconstrictors in patients with type 2 HRS has not been assessed</td>
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</table>
located on the basis of the MELD (model of end-stage liver disease) score, which is obtained by a formula including serum bilirubin, serum creatinine, and international normalized ratio (INR) [32, 33]. Patients with HRS have high MELD scores, patients with HRS type 1 being those with higher MELD scores. Whatever the system used for organ allocation, HRS should probably be treated before transplantation is done in an attempt to improve renal function. This step may help reduce the high morbidity and mortality after transplantation reported in patients with HRS than in those without HRS [10, 13]. Combined liver and kidney transplantation for patients with HRS does not improve the overall results obtained with liver transplantation alone and should not be used [34].

Other Therapeutic Methods
Renal replacement therapy (i.e. hemodialysis) has been used in the management of patients with type 1 HRS, especially those who are candidates for liver transplantation, in an attempt to maintain patients alive until liver transplantation is performed or an unlikely spontaneous improvement in renal function occurs [35]. Unfortunately, the potential beneficial effect of renal replacement therapy has not been unequivocally demonstrated. It is the clinical experience that most patients do not tolerate hemodialysis and develop important side effects, including severe arterial hypotension, bleeding, and infections that may contribute to death during treatment. Moreover, findings that indicate the need for renal replacement therapy (severe fluid overload, acidosis or hyperkalemia) are uncommon, at least in early stages of type 1 HRS. Therefore, the initial therapy for these patients should probably include measures aimed at improving circulatory function (i.e. vasoconstrictors) and not hemodialysis.

Drugs other than vasoconstrictors have been used for many years in the management of HRS despite their unproved efficacy. This holds true for drugs with renal vasodilator effect, such as dopamine or prostaglandins [35]. Several isolated reports suggested a beneficial effect of octreotide alone, a drug that inhibits the production of several vasodilator peptides of splanchnic origin, especially glucagon. However, a recent randomized, controlled study with 50 μg/h in infusion did not show any positive effect [36]. Finally, N-acetyl-cysteine showed efficacy in a short series of patients at a dosage of 300 mg/12 h, but these results need confirmation in larges series [37].

Recently, extracorporeal albumin dialysis (MARS), a system that uses an albumin-containing dialysate that is recirculated and perfused through a charcoal and anion-exchanger columns, has been shown to improve systemic hemodynamics and reduce the plasma levels of renin in patients with type 1 HRS. In a small series of patients a benefical effect with improved survival was reported. However, further studies are needed to confirm these findings [38].

**Management of Type 2 HRS**

Unlike patients with type 1 HRS, those with type 2 HRS can be managed as outpatients unless they develop complications of cirrhosis that necessitate hospital admission. The commonest clinical finding in these patients is refractory ascites. Diuretics should be given only if they cause significant natriuresis (i.e., urine sodium excretion of more than 30 mmol daily) [39]. Care should be taken with the use of spironolactone in these patients because the risk of hyperkalemia. Dietary sodium restriction (40–80 mmol per day) is important to decrease the ascites formation rate, since sodium excretion is severely impaired and most patients respond poorly or not at all to diuretics. Repeated paracentesis with intravenous albumin is probably the treatment of choice of large ascites in these patients. If dilutional hyponatremia is present, total fluid intake should be restricted to about 1,000 ml/day. Bacterial infections should be diagnosed and treated early to avoid the risk of precipitating type 1 HRS.

**Vasoconstrictors**

There are few data on the effectiveness of vasoconstrictors in type 2 HRS. Alessandria et al. [40] treated 11 patients with type 2 HRS with terlipressin and albumin. Normalization of serum creatinine was observed in 8 cases. However, in all of them, HRS reoccurred after discontinuation of therapy. These results should be confirmed in further studies.

**Transjugular Intrahepatic Portosystemic Shunts**

The use of TIPS in patients with type 2 HRS is associated with an improvement of renal function, better control of ascites, and reduced risk of progression to type 1 HRS [24, 40]. However, a subanalysis of patients with type 2 HRS included in a randomized study comparing TIPS and repeated paracentesis plus intravenous albumin in patients with cirrhosis and refractory ascites showed that the use of TIPS was not associated with improved survival compared with the other treatment [40]. Therefore, the beneficial effects of TIPS in reducing the rates of ascites recurrence and progression to type 1 HRS should be weighed against the lack of improvement in
survival, increased risk of encephalopathy, and high
costs.

Liver Transplantation

Liver transplantation is the treatment of choice for
patients with cirrhosis and HRS who are candidates for
the procedure because it allows the cure of both the liver
disease and the associated renal failure, which is reversible after transplantation [13]. The short survival of pa-
tients with type 2 HRS (median 6 months) should be tak-
ien into account when these patients are assessed for liver
transplantation.

Prevention

Two randomized controlled studies in large series of
patients have shown that HRS can be prevented in spe-
cific clinical settings. In the first study [41], the adminis-
tration of albumin (1.5 g/kg i.v. at infection diagnosis and
1 g/kg i.v. 48 h later) together with cefotaxime in patients
with cirrhosis and spontaneous bacterial peritonitis mark-
edly reduced the incidence of impairment in circulatory
function and the occurrence of type 1 HRS as compared
to a control group of patients receiving cefotaxime alone
(10% incidence of HRS in patients receiving albumin
33% in the control group). Moreover, the hospital mortal-
ity rate (10 vs. 29%) and the 3-month mortality rate (22
vs. 41%) were lower in patients receiving albumin. In a
second study [7], the administration of pentoxifylline
(400 mg t.i.d.) to patients with severe acute alcoholic hep-
atitis reduced the occurrence of HRS (8% in the pentoxi-
flyline group versus 35% in the placebo group) and hos-
pital mortality (24 vs. 46%, respectively). Since bacterial
infections and acute alcoholic hepatitis are two important
precipitating factors of type 1 HRS, these prophylactic
measures may decrease the incidence of this complica-
tion. Although the beneficial effects obtained in these two
clinical trials would ideally require confirmation in other
studies, they represent the first big step towards effective
prevention of HRS in patients with end-stage liver dis-
ase.

Prognosis

HRS is the complication with the worst prognosis of cirrhosis and its development is associated with a very
low survival expectancy. Spontaneous recovery is very
uncommon. A recent study has demonstrated that the
type of HRS and MELD score are the only independent
prognostic factors in HRS [Ginès, P., unpubl. obs.]. Pa-
tients with type 1 HRS have a hospital survival rate of
less than 10% and an expected median survival time of
only 2 weeks. In contrast, patients with type 2 HRS show
a much longer median survival time, which is of approx-
imately 6 months.

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