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Hepatorenal Syndrome

A Nephrologist's Perspective

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Biography sketch:

Dr. Henry Quinones earned his medical degree at the University of Puerto Rico Medical Sciences Campus in 1995. He completed his Internal Medicine Training at the VA Medical Center of San Juan, Puerto Rico in 1998. He came to UT Southwestern to complete an academic oriented nephrology fellowship. Upon completion of his clinical training, he joined the research laboratory of Dr. Orson W. Moe, where he spent 4 years of training in basic science laboratory techniques to study the following areas of nephrology: intrarenal dopamine system and its relation to the pathogenesis of Hypertension, the regulation of the proximal tubule Na/H exchanger-3, salt balance and risk of formation of kidney stones, kinetics of the amino acid transporters in the proximal tubule, klotho as a marker of AKI and as an earlier marker of GFR in chronic kidney disease. Dr. Quinones joined the Internal Medicine faculty in 2002. Currently, he is an Associate Professor of Internal Medicine at UT Southwestern Medical Center. He is the Medical Director of the Renal Clinics (Renal, CKD and Glomerulonephritis) and Acute Dialysis Unit at Parkland Memorial Hospital. He attends Internal Medicine wards as well as our nephrology inpatient services of Dialysis, Consult and Kidney Transplant. He enjoys teaching and was humbled a few years ago when he was recognized with the Outstanding Teaching Award in 2009.

This is to acknowledge that Henry Quinones, M.D. has not disclosed (any) financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Quinones will be discussing off-label uses in his presentation.

Hepatorenal syndrome is a group of clinical signs and symptoms occurring in the patient with liver cirrhosis or acute liver failure that include: functional form of acute renal failure in the absence of any clinical, laboratory or anatomical evidence of other causes of renal failure occurring in the setting of advanced liver disease with portal hypertension. The term functional renal failure entails a form of acute kidney injury that results from a physiologic response of the kidney to a decreased effective arterial blood volume from progressive peripheral splanchnic vasodilation. Other almost universal findings include hypervolemic hyponatremia with plasma sodium < 130, fractional excretion of Na << 1% and portal hypertension manifested with ascites. This form of functional renal failure is not responsive to intravascular volume expansion and is very characteristic of this syndrome.

The pathophysiology of this syndrome is described in **Fig. 1**. In the early stages of liver disease, moderate portal hypertension developes from increase resistance to flow through sinusoidal hepatic circulation, leading to modest splanchnic vasodilation mainly induced by increased local generation of vasodilators like Nitric Oxide and/or endotoxemia, which causes a modest decrease in effective arterial blood volume (EABV). In response to this decreased EABV, the heart will respond with increased heart rate and/or stroke volume, which increases cardiac output (CO), and this reestablishes EABV and maintains renal blood flow (RBF) and glomerular filtration rate (GFR) in the normal range. Also, a hepatorenal signal has been proposed as a potential explanation to the early decreased renal excretion of Na seen in these patients not explained by decreased EABV in early liver disease[1, 2], [3-9]

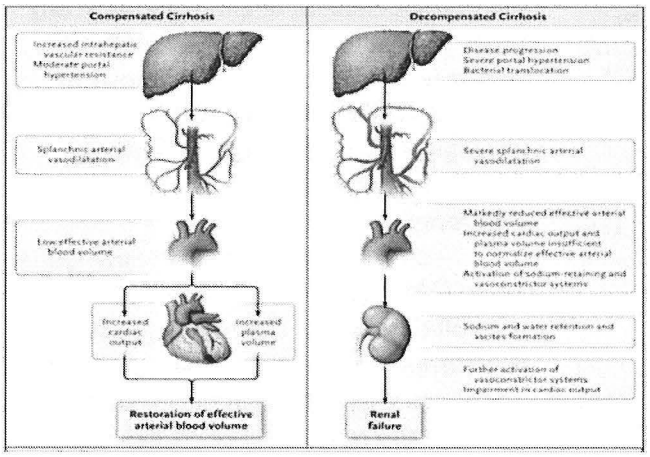


Fig. 1 Pathophysiology of Hepatorenal Syndrome

As the liver disease progresses to more advanced stages, portal hypertension will get severe and this will cause splanchnic vasodilation to become more severe and with this, the EABV decreases further. However, by this stage of liver disease, the patient would have developed cirrhotic cardiomyopathy (characterized by diastolic and systolic dysfunction), and the cardiovascular system will not be able to increase the HR and/or SV and/or CO and this will lead to activation of sympathetic nervous system, Renin angiotensin system, Tubuloglomerular feedback, Myogenic reflex and increased secretion of ADH, all in response to a non-reestablished decreased EABV. Activation of these systems, will lead to intense vasoconstriction of the renal vasculature causing a decrease in renal excretion of Na, RBF and GFR. This chronic renal vasoconstriction can be associated with a maladaptation of the myogenic reflex so that even when perfusion pressure is reestablished with IVF's the renal arteriolar vasoconstriction does not decrease and renal hypo-perfusion and decreased renal function persists which is a very characteristic feature of this form of functional renal failure **(Fig. 2)**.

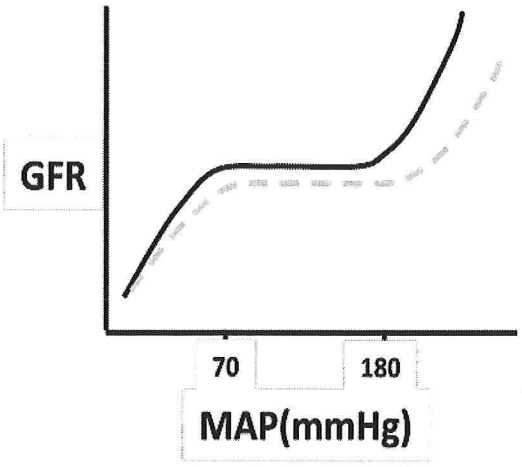
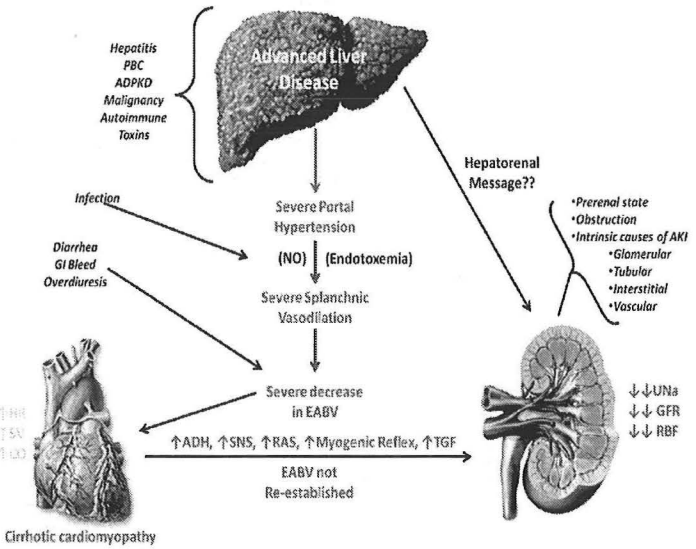


Fig. 2 Maladaptation of Autoregulation of GFR

The etiologies for the chronic liver disease are varied and can include diseases that can also lead to other forms of renal failure other than this functional renal failure associated to the hepatorenal syndrome **(Fig. 3)**. The vasodilation of splanchnic vasculature can also result from induction of NO synthesis from endotoxemia resulting from an infectious process and not only from portal hypertension.

Fig. 3 Etiology of Hepatorenal syndrome



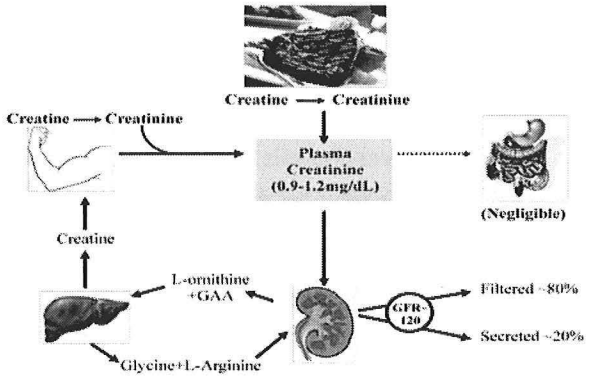
The severe decrease in EABV can result from gastrointestinal bleeding, shock, diarrhea and/or overdiuresis and not only in response to splanchnic vasculature vasodilation. Also, renal failure can result from pre-renal, post renal or intrinsic renal causes, and not only from a hepatorenal physiologic chain of events only, as in any other patient with AKI. So obviously, hepatorenal syndrome is a diagnosis of exclusion and all of these other potential etiologies should be ruled out before making the diagnosis of hepatorenal syndrome.

So we have to identify acute kidney injury (AKI) first, then rule out other possibilities, then make our diagnosis of Hepatorenal syndrome. Because we are dealing with a non-steady state situation of AKI, we cannot use the most used tests in the clinical area to estimate renal function. We cannot use creatinine clearance because the renal function in AKI is changing by the minute and by the time we end up with our 24 hr collection and get the results from it, the renal function is changed. Similarly we cannot use estimating formulas as these were derived, validated and recommended to be used in steady state situations and not non-steady state situations like in AKI. Even the gold standard tests for the measurement of GFR, inulin and/or iothalamate clearance, cannot be used to measure GFR in the setting of AKI as they also involve a timed collection of urine and by the time we get our results, the renal function will be changed and different. So, we are left with the plasma creatinine as our marker of AKI and single current clinical available marker of AKI including Hepatorenal syndrome.

Plasma creatinine is a very inaccurate and late marker of AKI including the hepatorenal syndrome. First, plasma creatinine is determined by means of the colorimetric assay alkaline picrate method. In this assay, creatinine in blood mixes with picrate in an alkaline environment and causes a change in color of the solution, strength of which is directly proportional to the plasma creatinine concentration. This colorimetric assay has negative interactions with some of the substances accumulated in blood of patients with chronic liver disease, like bilirubin. In the presence of bilirubin, the change in color of the picrate alkaline solution is less intense, leading to a false lower reading of the plasma creatinine concentration. So this is one of the reasons why patients with chronic liver disease have a low serum creatinine even in the setting of low GFR. This is also the case even when using other methods of determining serum creatinine like enzymatic methods.

Plasma creatinine is determined by multiple factors involved in the balance of production of creatinine and clearance of creatinine **(Fig. 4a)**. Protein intake, mainly in the form of meat contributes to the production of creatinine as cooking the meat and exposing it to heat will cause 50% of creatine (precursor of creatinine) get hydrolyzed non-enzymatically to creatinine which will be absorbed from gastrointestinal tract. Also, 2% of our creatine muscle mass is hydrolyzed non-enzymatically to creatinine every day with the absolute value mainly determined by the absolute amount of muscle mass. Additionally, the kidney and the liver share components of the ornithine metabolic pathway that results in the liver generating some creatine that is send and stored in the muscle and ultimately

Fig. 4a. Determinants of plasma creatinine:

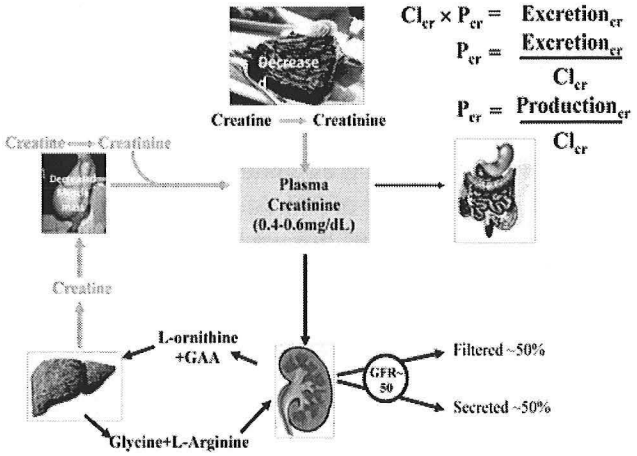


contributes to the total muscle creatine mass which determines the production of creatinine in muscle every day. These are all the factors that determine the production of creatinine in our system[10].

On the other hand, we have factors that determine the excretion of creatinine from our system. In the setting of normal kidney function, the gastrointestinal tract plays a negligible role in disposing of some creatinine. The main role in excreting creatinine happens in the kidney by means of filtration (80%) and tubular epithelia secretion (20%). The balance of the addition of creatinine and the excretion of creatinine determines the plasma concentration of creatinine[10].

In the setting of chronic liver disease and hepatorenal syndrome, the patient has a decreased intake of protein and meat, which decreases the production of creatinine and its addition to plasma **(Fig 4b)**. Also, total muscle mass is decreased, which reduces the absolute amount of creatine hydrolyzing to creatinine every day and getting mobilized from muscle to plasma every day. Additionally, in the setting of liver cirrhosis, the amount of creatine generated in the liver by means of the ornithine metabolic pathway decreases, contributing to a decrease in the absolute amount of creatine in muscle, which decreases the absolute amount of creatinine production in muscle and secretion into plasma. Obviously all of these processes lead to decrease production of creatinine contributing to a decrease plasma creatinine)[10].

Fig. 4b. Determinants of plasma creatinine in cirrhosis:



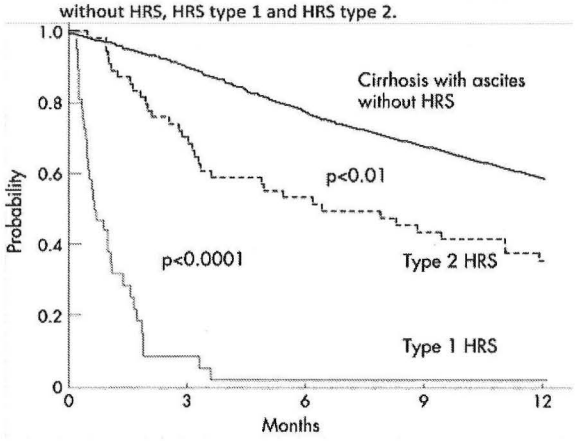
On the other hand, as the renal function decreases, the gastrointestinal tract gains a relevant role in disposing of a significant amount of creatinine by changing the gastrointestinal bacterial flora that can metabolize creatinine to other products. Finnally, a decrease in GFR, will be accompanied by and increase in secretion of creatinine by the renal tubules. The final result is increased in excretion of creatinine. The combination of decreased production of creatinine and increased excretion of creatinine will lead to a decreased plasma creatinine typical of patients with chronic liver disease and hepatorenal syndrome. So a decrease in GFR of more than 50% will be needed before we notice an elevation in the serum creatinine, that in the patient with liver cirrhosis and hepatorrenal syndrome could be just and elevation of serum creatinine to the upper level of normal. Therefore, serum creatinine is a very late marker of AKI in general and Hepatorenal syndrome. This is of very much importance as in AKI the earlier the diagnosis is made, the higher the probability of recovery and the lower the chance of development of irreversible renal damage, and the opposite is true too[10].

Using the rate of serum creatinine increase, hepatorenal syndrome have been classified into type 1 and type 2 **(Fig. 5)**. HRS type I is identified by an increase in serum creatinine to a value higher or equal to 2.5mg/dL in over a period of 2 weeks. It is associated to a precipitating event like gastrointestinal bleeding, spontaneous bacterial peritonitis, overdiuresis, diarrhea, large volume paracenthesis without albumin administration, urinary tract infection, pneumonia, etc. Also, in HRS type 1 the patient is usually hospitalized and has worse prognosis with a median survival of 2 weeks and mortality of > 90% in 3 months **(Fig. 6)**. HRS type II is identified by an increase in serum creatinine to a value of 1.5mg/dL in no longer than 2 weeks period, is not associated to a precipitating event, the patient is not hospitalized, and has better prognosis with medial survival of 6 months and mortality of 70% in one year **(Fig. 5 and Fig. 6)**. HRS type 2 seems to be the progressive course of HRS. HRS type 2 patients can convert into a HRS type 1. HRS type I and HRS type II are a spectrum of the same pathophysiologic processes [1, 2], [3-9].

Fig. 5 Types of HRS

HRS type I:	HRS type 2:
• ↑Scr to 2.5mg/dL in 2 weeks • Precipitating event • Hospitalized • Worse prognosis – Medial survival of 2 wks – Mortality>90% in 3 mo	• ↑Scr to at least 1.5mg/dL in longer then 2 wks • No precipitating event • Outpatient • Better prognosis – Medial survival of 6 mo – Mortality of 70% in 1 year

Fig. 6. Probability of Survival on patients with cirrhosis without HRS, HRS type 1 and HRS type 2.



Recognizing AKI at early stages is of great importance as the longer the time from injury to diagnosis, the higher probability of permanent renal damage and the lower the probability of renal function recovery and hepatorenal syndrome is not an exeption to this **(Fig. 7)**. Serum creatinine above the normal range is a late marker of AKI. At the moment we don't have a renal "troponin" but we have other potential ways of diagnosing AKI early like smaller increase in serum creatinine and/or biomarkers of AKI like Cystatin-C, NGAL, IL-18 and KIM-1[11-14].

Small increases of serum creatinine levels in hospitalized patients are associated with substantial morbidity and mortality. The Acute Dialysis Quality Initiative developed a consensus definition and classification of AKI based on creatinine increase and decrease in glomerular filtration

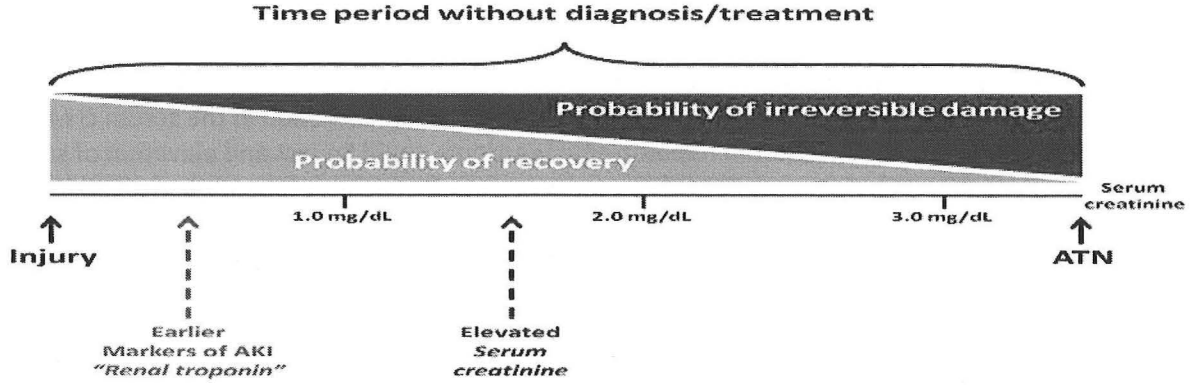


Fig. 7. Importance of early recognition of AKI

rate (GFR) or urine output: the RIFLE criteria. More recently, the RIFLE criteria were modified by the AKIN **(Table 1)**. The criteria are identical to the first three stages of RIFLE, with the exception of a shorter time frame of AKI within 48 hours, and a lower creatinine threshold of greater than 0.3 mg/dL from baseline to peak value **(Table 1)**.

Table 1. Acute kidney injury stages

AKIN stages	Serum creatinine increase from baseline	Urine output
Stage 1	↑ of ≥0.3mg/dL or ≥ 150 to 200%	< 0.5 ml/Kg/hr for > 6 hrs
Stage 2	> 200 to 300%	< 0.5 ml/Kg/hr for > 12 hrs
Stage 3	> 300% or >4mg/dL with acute ↑of ≥0.5mg/dL	< 0.3 ml/Kg/hr for ≥ 24 hrs or anuria ≥ 12 hrs

The prognostic values of the RIFLE and AKIN criteria have been validated for in-hospital mortality in numerous studies including cardiothoracic surgery, trauma, or critically ill patients and they provide a uniform definition of AKI. The utilization of this AKI staging or classification could be a better way of diagnosis AKI earlier and could potentially have positive effects in the diagnosis and therapy of AKI including the hepatorenal syndrome, but data proving evidence for this is lacking at the moment. The International Ascites Club will meet soon to revaluate the diagnostic criteria of Hepatorenal syndrome and plans to consider the AKIN staging or RIFLE classification of AKI for the early diagnosis of this form of AKI[11-13, 15].

Many biomarkers have been widely studied for use in the diagnosis of AKI because serum creatinine is an imperfect marker for the early and accurate diagnosis of AKI. A biomarker that is released into the blood or urine from the injured kidney soon after AKI may be an earlier marker of AKI than serum creatinine. Early diagnosis of AKI may result in more optimal dosing of antibiotics, avoidance of nephrotoxic agents, and earlier nephrology consultation. The most promising early biomarkers of AKI are interleukin-18 (IL-18), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and cystatin C **(Table 2)**.

Table 2. Biologic markers for the early diagnosis and prognostic stratification of AKI

Biomarker	Type/Time of injury
NGAL	Ischemic injury (2hrs)
KIM-1	Ischemic and nephrotoxic injury (12hrs)
Cystatin C	AKI in ICU
IL-18	Ischemic injury

In addition to being a mediator of AKI, IL-18 is also a biomarker of AKI. IL-18 is increased in the urine in mice with AKI. Urine IL-18 is increased in patients with AKI compared to other kidney diseases and in renal transplant patients with delayed graft function. Urine IL-18 increases 48 hours before a 50% increase in serum creatinine in critically ill adults with acute respiratory distress syndrome, children with AKI in the ICU, children that develop AKI post cardiopulmonary bypass, and in adults with contrast nephropathy [11-13, 15].

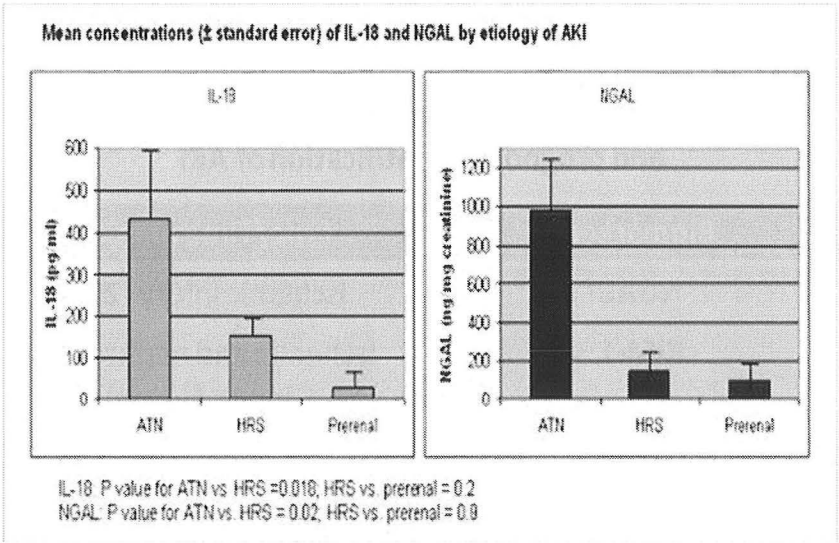
NGAL is a small protein of the lipocalin superfamily and is expressed by renal tubular cells. NGAL protein increases in the kidney and in the urine in early ischemic AKI in rats and mice, and in the early stage of cisplatin-induced AKI. NGAL increases in the urine before serum creatinine in children and adults with AKI post cardiopulmonary bypass, children with AKI in the ICU, and adults and children with contrast nephropathy. Urine and plasma NGAL predicts AKI in critically ill adults. Plasma NGAL concentrations obtained during surgery are highly associated with postoperative AKI in patients undergoing liver transplantation. A more recent meta-analysis of 12 adults and seven children studies

including cardiac surgery, contrast nephropathy, and critically ill patients demonstrated that plasma and urine NGAL levels appear to be of diagnostic and prognostic value for AKI [11-13, 15].

KIM-1 is an epithelial cell adhesion molecule that is expressed at a low level in normal kidney. KIM-1 is increased in the kidney in ischemic AKI in rats and mice. Urinary KIM-1 is increased in patients with acute tubular necrosis (ATN), and is a predictor of graft loss in kidney transplant patients. More recently, a rapid KIM-1 urine dipstick was developed for the early detection of kidney injury. In another study, it has been shown that a panel of urinary biomarkers including NGAL, N-acetyl-β-(D)-glucosaminidase and KIM-1 may improve the early detection of postoperative AKI after cardiac surgery before a rise in serum creatinine [11-13, 15].

A reasonable approach to the diagnosis of AKI, could be using a panel of urine and/or plasma biomarkers of AKI. All of them earlier markers of AKI, earlier than serum creatinine, and some of them markers of tubular injury, so that we can identify AKI earlier and discriminate between functional renal failure in hepatorenal syndrome from other etiologies like pre-renal azotemia and/or ATN which happens to be a common scenario encountered when approaching renal failure in the cirrhotic patient. Urine IL-18 and NGAL were measured in 27 cirrhotic patients with AKI (diagnosed using AKIN staging). A blinded review of their medical records was performed by a selected group of nephrologists and the patients were classified into pre-renal azotemia, hepatorenal syndrome or ATN. The urinary level of IL-18 and NGAL were plotted against diagnosis. Urinary IL-18 and NGAL discriminated in a statistically significant manner between ATN and HRS suggesting that urinary biomarkers of AKI can play a role in differentiating ATN from HRS. Pre-renal state was associated to the lowest urinary levels of both IL-18 and NGAL. This data suggest the fact that hepatorenal syndrome is a continuum process that goes from pre-renal state to possible ATN and urinary biomarkers of AKI will reflect this with low levels in pre-renal state, higher levels in ATN and intermediate levels for hepatorenal syndrome **(Fig. 8)**. Studies with a larger number of patients are needed to confirm these findings (J Am Soc Nephrol 2009; 20: 361A)

Fig. 8. Urinary NGAL and IL-18 in patients with ATN, HRS or Pre-renal state



In the absence of biomarkers of AKI in our current clinical practice scenarios, we end up, making our diagnosis of hepatorenal syndrome using serum creatinine and following our generic approach to AKI. First we look at clues from the history and/or physical exam that would indicate the patient has a decreased intravascular space. Then we will confirm our impression with tests like tilt test and FENa and look for hyaline cast in the urine sediment. Once this is ruled out, then we look at clues from the history and physical suggestive of obstructive uropathy and get a kidney US to either rule in or rule out this possibility. Last, we look for clues in the history and physical exam suggestive of either, a glomerulonephritis, vasculitis, interstitial or tubular process. We will need the help of a complete serologic work up and a good analysis of the urine sediment. Granular casts and tubular epithelial cells will increase the suspicions for a tubular problem like ATN. WBC and/or eosinophils will suggest an interstitial inflammatory process like acute interstitial nephritis. Microscopic hematuria, dysmorphic RBC's, RBC casts and proteinuria higher than 500 mg per day will suggest a glomerulonephritis process.

The presence of any of these findings suggestive of an etiology other than hepatorenal syndrome in the cirrhotic patient with AKI, will justify a kidney biopsy for diagnosis, prognosis and therapy.

Now, if we take a look to the diagnostic criteria for hepatorenal syndrome created by the International Ascites Club **(Fig. 9)**, we can realize of its useful points and limitations [4]. First, it clearly defines the population of affected patients by assuring the presence of cirrhosis and ascites. Unfortunately, it uses a serum creatinine of 1.5mg/dL or higher to diagnose this form of AKI which is clearly a late and innacurate marker of AKI in general, and specially in the setting of liver cirrhosis. It recommends lack of improvement of renal function after 48 hrs of Albumin IV administration to rule out pre-renal azotemia. The patient should have no signs of shock to make sure we ruled out pre-renal states or ATN resulting from hypotension. Also, no evidence of exposure to nephrotoxic agents should be clearly documented to rule out other forms of AKI that could result from drug exposure. A kidney sono should also document the abcense of obstructive uropathy. The presence of proteinuria higher than 500 mg per day and/or hematuria will increase the suspicions for AKI etiologies other than hepatorenal syndrome and a kidney biopsy should be considered in this situation.

Fig. 9 Diagnostic criteria for the Hepatorenal syndrome by the Internaational Ascites Club

- Cirrhosis with Ascites.
- Serum Creatinine > 1.5mg/dL.
- No improvement in serum creatinine after at least 48 hr of diuretic withdrawal and volume expansion with alb 1g/Kg/day or max of 100g/day.
- No evidence of shock.
- No current or recent treatment with nephrotoxic drugs.
- Absence of parenchymal (indicated by proteinuria >500 mg/day and/or microhematuria (>50 RBC/HPF) and/or obstructive renal disease.

Interestingly, in a study of 23 patients with cirrhosis with normal serum creatinine and proteinuria < 500 mg per day that got a kidney biopsy at the time of orthotopic liver transplantation the pathology revealed glomerular abnormalities in all patients. The glomerular abnormalitites included: hepatic glomerulosclerosis in 8 patients, membranoproliferative glomerulonephritis in 1 patient, IgA nephropathy in 2 patients, and minor glomerular abnormalities (mesangial hypercellularity, capillary wall wrinkling, thickening of glomerular basement membrane, focal tubular atrophy and double contour of capillary wall) in 12 patients. This shows that even in the setting of normal serum creatinine and no clinically significant proteinuria patients with liver cirrhosis can still have early histologic evidence of glomerular abnormalities, rendering serum creatinine as a very inaccurate marker of kidney disease[16].

On the other hand, when cirrhotic patients with AKI and urinary abnormalities received a kidney biopsy the etiologies included: Glomerulonephritis (24%), Pre-renal (22%), ATN (11%), HRS (8%), Nephrotoxic (3%) and infection episode (32%). This reinforces the importance of considering a kidney biopsy in patients with cirrhosis, AKI and abnormal urinary sediment [1].

A kidney biopsy is not only important to make a diagnosis of the etiology of AKI but it can also provide prognostic information about the particular renal diagnosis. Although, a percutaneous kidney biopsy is associated with increased risk of bleeding in a coagulopathic and cirrhotic patient, there is enough data to conclude that the transjugular approach can be done in a safe manner and obtain sufficient amount of tissue to make a diagnosis, determine therapy and determine prognosis. All the studies showing safety of transjugular approach for a kidney biopsy corrected coagulopathy with Vitamin K and/or FFP to achieve an INR of < 1.5 and transfused Platelets to achieve a platelet count of >50000/mL before performing the procedure[17-19].

There are a few clinical situations where hepatorenal syndrome can be prevented. The first one is administration of albumin IV improves systemic hemodynamics in patients with liver cirrhosis and spontaneous bacterial peritonitis. The second is the administration of albumin IV after a large volume

paracenthesis prevents postparacenthesis circulatory dysfunction. The third one is the administration of pentoxyfylline to patients with alcoholic hepatitis and a Maddrey discrimination factor ≥ 32 is associated with improved survival and decreased probability of development of HRS[20-22].

Once the diagnosis of HRS is made there are several therapies we can consider. One of them is Vasoconstrictors like Telsipressin, Midodrine with Octeotride and Norepinephrine, all given together with IV Albumin. These agents can have a vasoconstrictive effect on the splanchnic vessels which can help re-establish EABV and subsequently reverse HRS. Albumin IV is not only utilized to have an effect in intravascular and effective arterial volumes but also for the many other functions albumin such as: antioxidant, ligand binding, transport molecule and pro-oxidant. Transjugular intrahepatic portosystemic shunts could be used as a way of decreasing portal hypertension and by means of this decrease splanchnic vasodilation. An artificial replacement of liver functions, like when using the molecular absorbent recirculation system, may resolve the hepatorenal milieu and improve circulatory and renal hemodynamics. Finally, but most importantly, the most effective way of treating HRS is a liver transplantation. We will discuss each one of these therapeutic alternatives in detail as follows.

The proof-of-concept studies using a vasopressin analog in the management of HRS-1 employed ornipressin. Complete response defined as either serum creatinine falling to less than 1.5 mg/dL or doubling of creatinine clearance to greater than 40 mL/min was observed in 57% to 75% patients with HRS-1. Median survival was prolonged to several months. However, because of the development of severe adverse events of an ischemic nature, ornipressin is not generally recommended for patients with HRS. One of the most studied vasopressin analogs in HRS is terlipressin. Because terlipressin is a pro-drug, the active metabolite, lysine-vasopressin, is gradually released over several hours, thereby avoiding many of the ischemic side effects without any compromise of its potency. Its longer half-life also allows for more convenient intermittent intravenous dosing. There is no standardized dosing schedule for terlipressin administration because of the lack of dose-finding studies. Terlipressin is generally started at a dose of 1 mg every 4 to 6 hours and increased to a maximum of 2 mg every 4 to 6 hours if there is no reduction in serum creatinine of at least 25% compared with the baseline value on day 3 of therapy. Treatment is maintained until the serum creatinine has decreased below 1.5 mg/dL. Response to therapy is characterized by a slowly progressive reduction in serum creatinine to below 1.5 mg/dL, and an increase in mean arterial pressure, urine volume, and serum sodium concentration. Median time to response is 14 days and the response time is usually dependent on the pretreatment serum creatinine level, being shorter in patients with lower baseline serum creatinine levels. Recurrence after withdrawal of therapy is uncommon and retreatment with terlipressin is generally effective. It is important to emphasize that most studies excluded patients with known severe cardiovascular or ischemic conditions or patients with ongoing sepsis. In most studies, terlipressin was given in combination with albumin (1 g/kg of body weight on day 1 followed by 40 g/d) to improve the efficacy of treatment on circulatory function[23-30].

Several small studies involving a total of 46 patients with HRS examined the effects of terlipressin, with or without albumin, on systemic hemodynamics and renal function. Terlipressin, given at an initial dose of 0.5 to 1.0 mg every 4 to 6 hours, and titrating upward to 2.0 every 4 to 6 hours significantly improved mean arterial pressure by 13% to 28%. Serum creatinine reduced by at least 50% and the GFR doubled. In the 2 studies that measured plasma renin activity, the levels were reduced by at least 80%, suggesting that terlipressin improved the EABV and reduced the activation of the systemic vasoconstrictor systems. Ischemic side effects were significantly less with terlipressin than with ornipressin **(Table 3)** [23-30]

Two larger, randomized, controlled trials were subsequently published on the use of terlipressin for the treatment of HRS-1. In the first, Sanyal and the Terlipressin Study Group evaluated the safety and efficacy of terlipressin plus albumin versus albumin alone in 112 patients with HRS-1 in a multinational study. Patients in the terlipressin group achieved significant improvement in serum creatinine, mean day-14 Model of End-stage Liver Disease score and HRS reversal compared with the placebo group. However, there was no difference in 6-month overall survival or transplant-free survival. More patients in the terlipressin group experienced serious adverse cardiac events such as nonfatal myocardial infarction, nonsustained supraventricular tachycardia, and arrhythmias (10 vs 4 patients). In the second study, Martín-Llahí and The Terlipressin and Albumin for Hepatorenal Syndrome Investigators compared terlipressin at 1 to 2 mg every 4 hours plus albumin to albumin alone in both HRS-1 and HRS-2 patients. Similarly, in this trial, the terlipressin group experienced a significantly higher rate of improved renal function. Survival at 3 months, however, was not different. Once again, there was an increased rate of cardiovascular complications in the terlipressin group including myocardial ischemia, intestinal ischemia, arrhythmias, and volume overload (5 vs 1 patient). The improvement in renal function after the administration of terlipressin in HRS-1 can be explained by its physiologic actions. Its vasoconstrictive effects on the systemic circulation can lead to an improvement in systemic hemodynamics, associated with an amelioration of the hyperdynamic circulation in cirrhosis. The EABV becomes better filled, as reflected by a significant reduction in activities of the renin–angiotensin–aldosterone system and SNS. This in turn, leads to an improvement in GFR, and renal sodium excretion. There is preliminary evidence that when terlipressin is given as a continuous infusion rather than as boluses in the treatment of HRS-1, the same efficacy can be achieved with a lower total daily dose and with fewer side effects. Pharmacodynamic studies have shown that continuous infusion of terlipressin provides a more sustained portal pressure-lowering effect than bolus injections, thereby explaining the beneficial effects of a terlipressin infusion over bolus injections. Although these studies have included a few patients with HRS-2, the data are difficult to abstract to determine the effects of terlipressin on renal function in patients with HRS-2. Studies specifically designed for HRS-2 patients are scant. However, given the fact that the pathophysiology of HRS-2 is similar to that of HRS-1, especially in terms of the splanchnic and systemic hemodynamic changes, there is every reason to believe that terlipressin should also work in patients with HRS-2. In a small study that included 11 patients with HRS-2, terlipressin given at a dose of 1 mg every 4 hours for at least 7 days resulted in a reduction in serum creatinine in 73% of patients, with 88% of the responders achieving a serum creatinine of less than 1.5 mg/dL. Seven of the responders then went on to receive a transjugular intrahepatic portosystemic shunt (TIPS), making it difficult to assess whether HRS-2 recurred after completion of terlipressin therapy or not **(Table 3)**. [23-30]

Table 3
Terlipressin + Alb IV
(Until Scr <1.5 or max 14 days)

Outcomes	Retrospective and Prospective cohorts	Randomized prospective controlled trials	Meta-analysis of RCT's
Renal function	↓Scr, ↑UOP, ↑GFR	↓Scr, ↑UOP, ↑GFR	↓Scr, ↑UOP, ↑GFR
Hemodynamic	↑MAP	↑MAP	↑MAP
Markers of low EABV	↓PRA, ↓Aldo, ↓NE, ↓ADH	↓PRA, ↓Aldo, ↓NE, ↓ADH	↓PRA, ↓Aldo, ↓NE, ↓ADH
Patient survival	Responders > non-responders	Control or placebo = treatment	Increased short-term

The most widely used α-adrenergic receptor agonist is midodrine, a systemic vasoconstrictor that has been approved for the treatment of postural hypotension. The acute effects of midodrine on renal function was first assessed in 25 cirrhotic patients with ascites (17 patients without HRS and 8 with HRS-2). In patients without HRS, midodrine was able to improve systemic and renal hemodynamics, increase urinary sodium excretion, associated with a decrease in plasma rennin activity, and arginine vasopressin, as well as serum nitrite and nitrate levels **(Table 4)**. However, in the 8 patients with HRS, midodrine did not have any significant effects on renal function, or urinary sodium excretion. However, the combination of midodrine and octreotide in patients with HRS-1 seems to have the same beneficial effects on renal function as midodrine alone in patients without HRS. Three studies, totaling 79 patients reported HRS reversal as defined by a serum creatinine of less than 1.5 mg/dL in 49% of patients when the combination was given for a median period of 17 days. Midodrine has been administered orally at an initial dose of 5 to 10 mg 3 times per day, and octreotide either subcutaneously at an initial dose of 100 μg 3 times daily, or as an intravenous infusion at an hourly dose of 25 μg/h after an initial bolus of 25 μg. If there is no increase in MAP of at least 15 mmHg, the dose of midodrine can be increased up to 15 mg 3 times daily and that of subcutaneous octreotide up to 200 μg 3 times daily. Another retrospective study evaluated the use of 7.5 to 15 mg midodrine combined with subcutaneous octreotide 100 to 200 μg 3 times per day and intravenous albumin 50 to 100 g/d for a mean of 8.4 ± 9.6 days in 75 patients with either HRS-1 or HRS-2. The treatment group was compared with a pre-2001 historical control group of 87 patients with either HRS-1 or HRS-2 who did not receive the drug regimen. During a mean follow-up of almost 4 months, there was a significant improvement of GFR in the treatment group compared with the historical controls. Median survival was significantly improved in patients who received the combination therapy for both HRS-1 and HRS-2 patients. The percentage of patients who underwent transplantation was increased only for patients with HRS-2. One study found that the dose of midodrine was an important determinant in HRS-1 reversal. When midodrine was given at 15 mg 3 times daily, 88% patients had HRS-1 reversal compared with 33% in those receiving >12.5 mg 3 times daily. Adverse events associated with midodrine use are generally mild and self-limiting and these include diarrhea and tingling without cardiovascular complications. Therefore, the combination of midodrine and octreotide is an alternative in the management of HRS, particularly in countries where terlipressin in unavailable. [31-34]

Table 4
Midodrine + Octeotride + Alb IV

Outcomes	Retrospective and Prospective cohorts
Renal function	↓Scr, ↑UOP, ↑GFR
Hemodynamic	↑MAP
Markers of low EABV	↓PRA, ↓Aldo, ↓NE, ↓ADH
Patient survival	Treated > non-treated at 30 days

NE (at 0.5–3 mg/h) is another α-adrenergic receptor agonist that has been administered to patients with HRS because of its potent vasoconstrictive effects on both the venous and arterial vasculature **(Table 5)**. However, the number of patients treated with NE is small and no randomized, comparative studies with a control group of patients receiving no vasoconstrictor therapy have been performed to evaluate its efficacy. The initial uncontrolled pilot study using NE showed a 83% reversal of HRS-1 in 12 patients after a median duration of treatment of 7 days. NE also effectively improved serum sodium concentration, creatinine clearance, urine output, and renal sodium excretion. Systemic hemodynamics as indicated by mean arterial pressure, and fullness of the EABV, as indicated by plasma renin activity, and aldosterone levels also improved. [35-38]

Two recent studies that were part of small, prospective, open-label, randomized studies of NE versus terlipressin found both vasoconstrictors to be equally effective in the treatment of HRS-1 with similar rates of side effects **(Table 5)**. One study compared the efficacy of NE versus terlipressin for treating HRS in 22 patients (9 with HRS-1 and 13 with HRS-2). Patients received norepinephrine 0.1 to 0.7 µg/kg per minute plus albumin (n = 10) or terlipressin 1 to 2 mg every 4 hours plus albumin (n = 12) for up to 2 weeks. Reversal of HRS occurred in 70% of patients receiving NE versus 83% of patients receiving terlipressin, indicating NE was not inferior to terlipressin in the management of HRS, although it was a small trial. Relapse after treatment discontinuation occurred in 29% of NE responders versus 60% of terlipressin responders. The cost of NE therapy was significantly lower than that of terlipressin. To evaluate the efficacy of NE for treating patients with HRS-1, a randomized pilot study was conducted using NE infusion starting at 0.5 mg/h with stepwise increases of 0.5 mg/h every 4 hours titrated to the mean arterial pressure plus albumin (20 patients) versus intravenous terlipressin 0.5 to 2 mg every 6 hours plus albumin (20 patients). NE significantly increased MAP (mean, 78.3–93.3 mmHg; *P*=.01), increased urine output (mean, 479–1278 mL/d; *P*=.01), and decreased serum creatinine from baseline (mean, 3.3–1.0 mg/dL; *P*=.01). The renal function improvement between patients treated with NE and those treated with terlipressin was similar. The percentage of patients who responded to therapy was not different between the NE and terlipressin groups (50% vs 40%; *P* = .741), and no difference was noted in cumulative survival between groups (11.6 vs 12.6 days; *P* = .452). At doses of 1.5 mg/h, NE has been associated with ventricular arrhythmias (7%) and myocardial hypokinesia (5%), both reversed with dose reduction. Given the much lower cost and wider availability of NE, it can be considered a safe and effective alternative to terlipressin for HRS-1, especially in countries where terlipressin is not available or cost is a major concern. However, patients being given NE should be transferred to an intensive care unit where it can infused in a monitored environment. [35-38]

Table 5
Norepinephrine + Alb IV
(7-14 days of Therapy)

Outcomes	Pilot studies Prospective cohorts	Randomized prospective non-controlled trials (T+A vs NE+Alb)
Renal function	↓Scr, ↑UOP, ↑GFR	↓Scr, ↑UOP, ↑GFR
Hemodynamic	↑MAP	↑MAP
Markers of low EABV	↓PRA, ↓Aldo, ↓NE, ↓ADH	↓PRA, ↓Aldo, ↓NE, ↓ADH
Patient survival	Responders>non-responders	Responders > Non-responders T+A = NE+A

Octreotide is a long-acting somatostatin analog that reduces portal hypertension and splanchnic hyperemia, and it may also cause splanchnic vasoconstriction; however, these effects may be blunted in patients with cirrhosis. Octreotide was evaluated in a randomized, double-blind, placebo-controlled, crossover study of 19 patients with either HRS-1 or HRS-2. Patients received intravenous octreotide 50 µg/h or placebo with daily albumin of 50 g over two 4-day study periods. Of the 14 patients who completed both crossover periods of the study, no significant differences were noted in the number of patients who had a 20% decrease in serum creatinine from baseline or reductions in plasma renin activity, aldosterone levels, or glucagon levels. No adverse effects related to octreotide therapy were observed. A retrospective review of 43 patients with HRS also found no clear benefit with octreotide monotherapy or any additional benefit when added to vasopressin. Based on the currently available literature, octreotide monotherapy does not seem to be any more effective than placebo for treating HRS. Octreotide is well-tolerated and may be useful when given as an adjunct therapy in patients with esophageal variceal hemorrhage or as a combination therapy with midodrine.

To date, there are no meta-analyses combining all studies using various vasoconstrictors to answer the question as to whether vasoconstrictors can reverse HRS; the number of randomized, controlled trials is small, and many of the studies only included small number of patients. However, there are 2 recent meta-analyses assessing the efficacy of terlipressin in the treatment of HRS. The first meta-analysis assessing 4 randomized, control trials demonstrated that the use of terlipressin plus

albumin was superior than albumin with or without placebo in improving renal function in patients with cirrhosis, ascites, and HRS-1. Reversal of HRS-1 defined as a reduction of serum creatinine to <1.5 mg/dL was observed in 46.0% of patients who received terlipressin plus albumin versus 11.6% in the control group. The improvement was sustained in most patients during the follow-up of 90 to 180 days, and recurrence only occurred in 8% of patients. There was also a trend toward improved transplant-free survival. Prolongation of treatment beyond 7 days and up to 20 days seems to improve the likelihood of response. Overall, terlipressin seemed to be safe and well-tolerated.

A second systematic review of randomized studies using all vasoconstrictors performed a subanalysis on the efficacy of terlipressin as a treatment for HRS, and found that terlipressin plus albumin was more efficacious than albumin alone in terms of improving renal function or reversal of HRS. The same study also reported that, when all randomized trials on vasoconstrictors alone or with albumin versus no intervention or albumin for HRS were assessed in a meta-analysis, there was a reduction in all-cause mortality favoring the vasoconstrictors. Currently, a multicenter trial is being conducted to confirm whether terlipressin increases survival in HRS-1 patients. Finally, treatment with vasoconstrictors in patients with HRS-2 is also associated with an improvement in renal function, but the recurrence rate is high. Nevertheless, the published information is still limited for vasoconstrictors to be routinely recommended as a treatment for HRS-2.

Despite the fact that the meta-analyses found that vasoconstrictor therapy was beneficial for patients with HRS, not every patient treated with vasoconstrictor therapy responded with an improvement in renal function. The identification of those patients who will not respond to vasoconstrictor therapy is critical when planning for other treatment options, especially for those patients awaiting liver transplantation. Predictors of response to terlipressin were recently investigated in a study of 39 consecutive cirrhotic patients with HRS-1 treated with terlipressin plus albumin. Eighteen patients (46%) responded to treatment. Multivariate analysis showed that the predictive factors for HRS reversal, defined as a decrease in serum creatinine to less than 1.5 mg/dL (133 _mol/L), included a baseline serum bilirubin level of less than 10 mg/dL and an increase in mean arterial pressure of more than 5 mmHg on day 3 of treatment. Another multicenter, randomized, double-blind, placebo-controlled trial of terlipressin for HRS-1 showed that only patients with baseline serum creatinine below 5.6 mg/dL and receiving more than 3 days of terlipressin therapy achieved HRS reversal. The corollary from these observations is that patients with severe liver and renal dysfunction should not receive terlipressin, because they are less likely to respond, especially if they do not have a hemodynamic response in the first 3 days of treatment. [39]

Table 6: TIPS
(Alone or post Vasoconstrictor Therapy)

Outcomes	Prospective cohorts
Renal function	↓Scr, ↑UOP, ↑GFR
Hemodynamic	↑MAP
Portal Hypertension	Decreased by 50%
Markers of low EABV	↓PRA, ↓Aldo, ↓NE, ↓ADH
Patient survival	TIPS > no TIPS

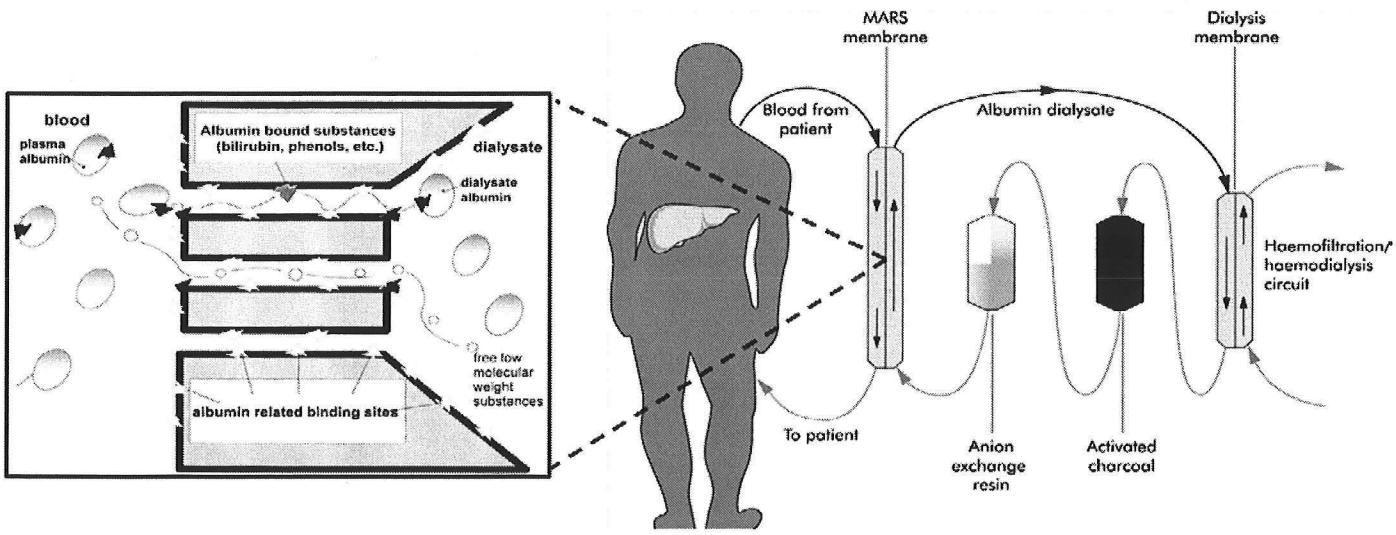
Because the use of vasoconstrictor therapy does not correct the renal dysfunction in every case of HRS, the addition of a treatment option that corrects another aspect of the pathophysiology of HRS would be a feasible alternative. The combination of vasoconstrictor therapy followed by a TIPS is one such alternative. The combination eliminates portal hypertension and reduces the extent of systemic arterial vasodilatation, and potentially could have an additive effect in improving renal function in patients with HRS **(Table 6)**. Midodrine, octreotide, and albumin were administered to 14 patients with HRS-1, and this improved but not normalized the renal function. Among those patients who were deemed suitable to receive a TIPS, the insertion of TIPS eventually normalized renal function over the course of 12 months and allowed eventual elimination of ascites. The overall survival rate was 50%, with the longest patient surviving 30 months. In another study, 11 patients with HRS-2 received terlipressin together with albumin, which maintained the central

venous pressure to 10 cmH2O. The placement of TIPS in 9 of the 11 patients eventually brought the serum creatinine down to 1.36 ± 0.3 mg/dL at 1 month post-TIPS. As expected, TIPS improved 24-hour urinary volume in all patients, leading to a lower post procedure diuretic requirement. Ascites also significantly decreased in all patients and eventually disappeared from the second week onward after TIPS. [35, 40-42]

The molecular absorbent re-circulating system is a new method that combines the efficacy of sorbents to remove albumin-bound molecules with the biocompatibility of the modern dialysis membrane **(Fig. 10)**. It is selective in removing protein-bound molecules that use albumin as a specific toxin carrier in human blood. Thus, albumin dialysis is an extracorporeal liver support system based on the concept of dialysis, using a specific membrane (Teraklin AG, Rostock, Germany, cut-off 50,000, sieving coefficient for albumin less than 0.01) and albumin as the dialysate. The albumin acts as a specific molecular adsorbent that is regenerated on-line by re-circulating in a recycling system (i.e., molecular adsorbents recycling system, or MARS, trademark of Teraklin AG, Rostock, Germany). Due to the attracting effect of albumin, the system achieves high clearance of albumin-bound substances such as bile acids and bilirubin, which are not removed by hemofiltration. The membrane used in MARS is capable of releasing the albumin-ligand complex present in the blood due to its physicochemical ability to interact with lipophilic binding domains. The membrane itself is impermeable to albumin and other valuable proteins such as hormones, clotting factors, and antithrombin III and is highly tolerated in clinical use. The two sorbent columns and the dialyzer allow the removal of both protein-bound and water-soluble toxins, thus making the system useful for patients with liver failure complicated by renal insufficiency. Furthermore, additional organ support is provided by maintaining electrolyte, acid/base, fluid balance, glucose level, and by removing ammonia, a watersoluble toxin that accumulates in liver failure. (49-57 Skeens, Semba et al. 1995; Guevara, Gines et al. 1998; Brensing, Textor et al. 2000; Michl, Gulberg et al. 2000[43-46]

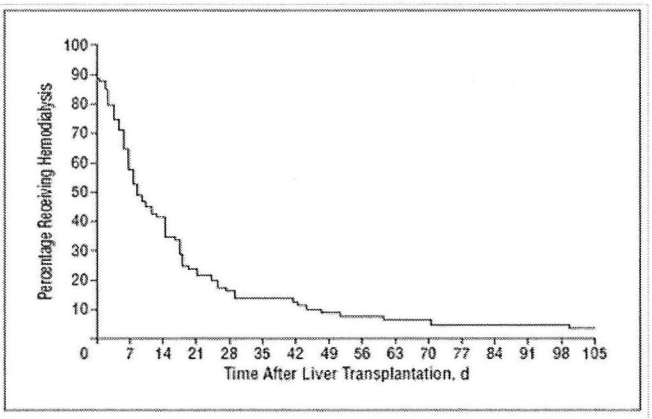
Two centers participated in the first prospective, randomized controlled trial to investigate the influence of albumin dialysis using MARS in patients suffering from end-stage liver disease and hepatorenal syndrome Type-I. All patients were Child Turquotte Class C and had elevated serum bilirubin (mean serum bilirubin >20 mg/dl). All 13 patients were oliguric or anuric and had a urine sodium <20 mmol/L, despite having adequate intravascular volume (CVP 10 mm Hg). Patients were randomized to standard medical therapy including hemodiafiltration or MARS treatment. MARS treatment was well tolerated and resulted in a significant removal of bilirubin as a marker for albumin-bound molecules. Furthermore, kidney function and creatinine levels also improved significantly in the MARS group compared to the control group. Associated with all these physiological improvements, a prolongation in survival time was achieved in the MARS group and was statistically significant. The hemodynamic effects of the MARS treatment in end-stage liver disease were investigated in another trial. Eight patients suffering from acute decompensation of chronic liver disease received a single MARS treatment. All patients were Child Turcotte Class C and had a serum bilirubin higher than 15 mg/dl. Five

Fig. 10. Molecular absorbent recirculation system



patients had hepatorenal syndrome as well. After the treatment, the mean bilirubin was reduced to 65.4% and creatinine to 48.4% compared to baseline. There was a statistically significant improvement in the mean arterial pressure resulting from an increase of systemic vascular resistance. The hemodynamic improvement was associated with the reduction in plasma renin activity [71-74].

Fig. 11 % of patients with HRS on dialysis after LTA



All of these therapies for HRS discussed so far can only serve the purpose of bridging the patient to the definitive therapy of HRS which is liver transplantation.

Liver transplantation is the definitive treatment for patients with HRS, because it eliminates liver dysfunction, portal hypertension, and the hemodynamic abnormalities in decompensated cirrhosis, which are central to the pathogenesis of HRS. Indeed, renal function improves in many patients with HRS after liver transplantation, associated with reductions in systemic vasoconstrictor levels. The majority of patients with HRS that receive an orthotopic liver transplant are receiving renal replacement therapy (RRT) by the time of transplantation with the great majority recovering renal function and come off of RRT in one to three months post-transplantation **(Fig 11)**. The need for RRT has increased along with waiting time in OLTx patients. Patients developing the need for RRT postoperatively have an increased 90-day mortality and lower 1-year survival with the highest being present in patients receiving CVVHD post operatively. **(Table 7)**. Some studies have shown that the renal function of patients with HRS post OLTx improves with time and by the 4th year or 13th year post OLTx the GFR is very similar to the GFR achieved by patients with cirrhosis, no HRS and post OLTx **(Fig. 12 and Table 8, respectively)**.

Table 7. Actual 1-year survival of OLTx patients

Timing of RRT	Patients	Survival	Survival %
Pre and post Tx RRT	19	14	73.6
Post Tx RRT	43	18	41.8

Fig. 12 Renal function post Liver transplant only in HRS and non-HRS patients:

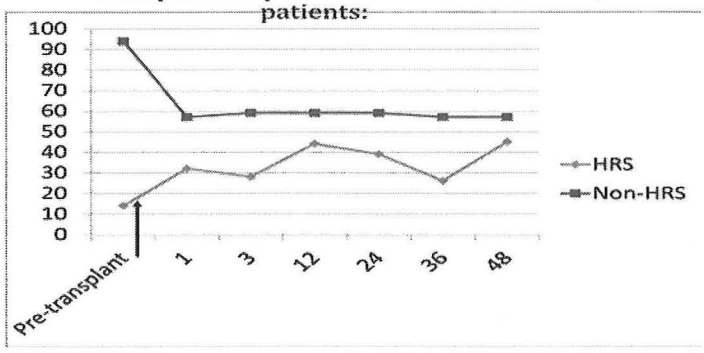
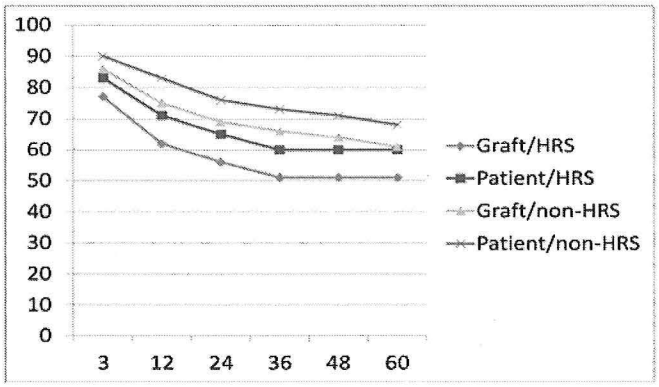


Table 8. Renal function post Liver transplant only in HRS patients:

HRS patients S/P OLTx (At 13 years)		
No CRF or ESRD	CRF(Scr>2.5 in 2X)	ESRD
92 (80.7%)	9 (7.9%)	13 (11.4%)

Fig. 13 Actuarial Patient and graft survival after Liver Transplant only in HRS vs no-HRS:



Patient and graft survival is lower for HRS patients vs non-HRS patients undergoing OLTx **(Fig. 13)**.

Therapy with Terlipressin and Albumin IV or Midodrine and Octeotride of HRS patients awaiting OLTx, is associated with improved patient survival that in non-HRS patients **(Fig. 14)** [43].

How can a kidney sustain so much insult with a sustained and progressive decrease in RBF and GFR and still have this amazing capability of surviving this insult and still regain renal function when the HRS pathophysiologic processes are reversed with a Liver Transplant alone? The answer to this question is speculative but the kidney make 0.5% of the body mass but still gets 22% of cardiac output. With the help of the anatomical arrangement of the vasa recta the kidney is the only organ where the venous O2 saturation is the highest. In the setting of HRS induced low GFR, the reabsorptive work of the renal epithelia in the nephron decreases as there is less absolute amount of solute filtered to reabsorb, and this decreases O2 consumption. A decreased RBF as in HRS will cause a decrease in O2 delivery to the kidney but the decrease on O2 consumption from low GRF may allow for the cells to tolerate the hemodynamic insult from HRS and this may be the reason why the renal function comes back in the majority of the patients with HRS that undergoes OLTx. In other words, the kidney is in a state of "hibernation" **(Fig 15)**. Kidneys from patients with HRS have been transplanted into non-HRS patients with success and the kidneys recovering and offering good levels of renal function. This is not unique of kidneys in humans. The hibernating bear does not eat or drink for 4-5 months during the winter time and produces no urine during this period of time. Its serum creatinine goes from 1.0-1.5 mg/dL baseline during the rest of the year to 3.0 mg/dL during hibernation in the winter time. This is the result of reduced renal blood flow and glomerular filtration rate during hibernation. Yet its kidneys are able to recover after 4-5 months of reduced renal blood flow and glomerular filtration rate. Another analogous example of this is the cardiorenal syndrome where in the setting of cardiac pump failure, physiologic vasoconstrictive mechanisms are

Fig. 14 Vasoconstrictor therapy pre-Liver Transplant:

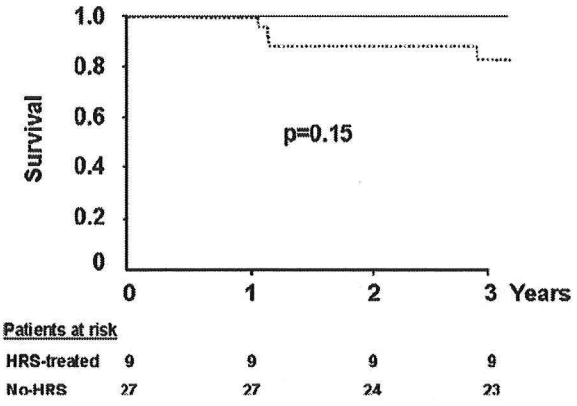
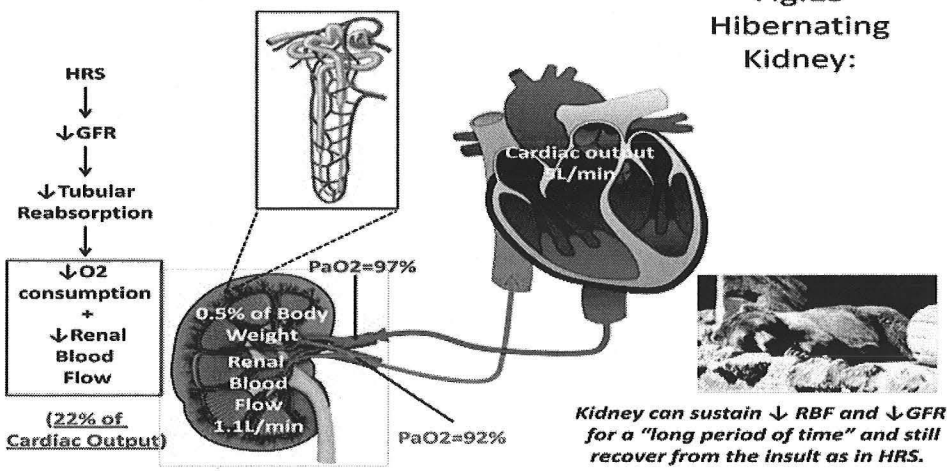


Fig.15 Hibernating Kidney:



Kidney can sustain ↓ RBF and ↓GFR for a "long period of time" and still recover from the insult as in HRS.

activated in the kidney leading to severe vasoconstriction of renal vessels leading to decreased renal blood flow and paralleled reduced glomerular filtration rate. Improvement of cardiac pump function with medications, artificial pumps or cardiac transplant can result in reversal of vasoconstriction and improvement in renal blood flow and glomerular filtration rate and ultimate improvement in renal function.

Table 9. Course of HRS type I post Liver transplant alone:

HRS type I Post OLTx		
	HRS resolved	HRS not resolved
	16	5 CKD 7 ESRD
Age	49	56
ETOH	3	8
Day 7 Bilirubin	6	10.1
Post-Tx Dialysis (d)	7	11

However, renal recovery after liver transplant is not guaranteed; small studies of particular Liver transplant centers documented up to 25% of patients remain dependent on renal dialysis after liver transplantation **(Table 9)**. Obviously, the majority of HRS patients will recover renal function but a significant number of patients may not recover renal function and stay on dialysis but we don't know how to determine who will and who won't recover renal function after a liver transplant alone. We don't have a good marker of irreversibility of renal damage in the setting of HRS either. One study have suggested duration of renal replacement as a marker of irreversibility of renal damage in the setting of AKI by documenting improved patient survival after a combined Liver and Kidney transplantation in HRS patients on dialysis for longer than 8 weeks compared to Liver transplant alone in HRS patients on dialysis for less than 30 days or CLKTx in HRS patients on dialysis less than 8 weeks **(Table 10)**. Therefore, it has been proposed that patients who have had more than 8 to 12 weeks of dialysis should be considered for CLKT. The issue of whether to perform CLKT is difficult. HRS itself is not an indication for CLKT as HRS is a form of AKI with good chances of renal function recovery in the setting of OLTx. CLKT is reserved for those patients with irreversible kidney injury, requiring hemodialysis for longer than 6 to 8 weeks, or progressive primary kidney disease. This have been challenged by the report of cases of patients with HRS on HD for up to 4-8 months that received CLKTx and later required a renal scan showing equal contributions of the native and renal allograft to the total renal function estimated by radioisotopes suggesting that HRS is potentially reversible even when dialysis have been used for longer than 8 weeks and also suggesting dialysis duration is a very poor marker of irreversibility of renal damage. In my opinion, to determine reversibility of renal damage we need a kidney biopsy in patients with HRS awaiting OLTx on dialysis for longer than 8 weeks before we consider them for CLKTx. Another potential area to consider is the use of biologic markers of AKI as markers of irreversibility of renal damage. Because the outcome after CLKT is inferior to that of liver transplant alone, there is now a trend to perform a liver transplantation, alone even in the presence of pretransplant renal failure requiring dialysis, and then only to consider kidney transplant if there is no renal recovery after liver transplantation [47, 48].

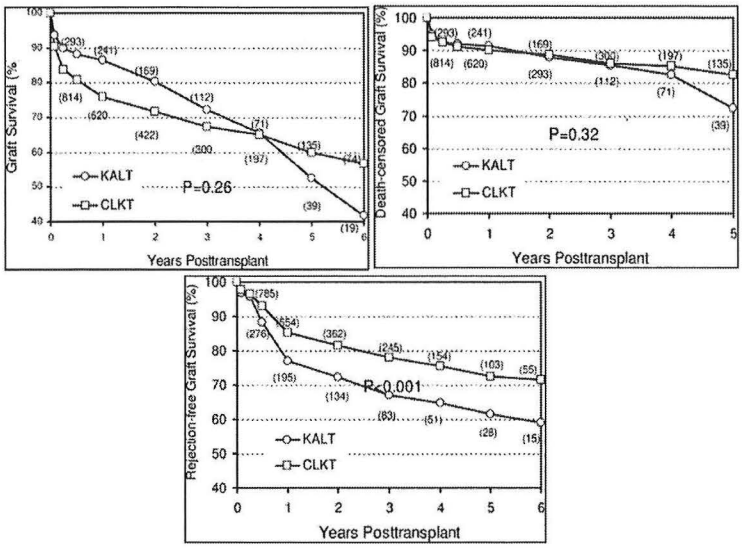
Table 10. Outcome of HRS by Pre-transplant dialysis duration:

Group	Liver transplant alone	Simultaneous Liver-Kidney Transplant	
Number	80	14	8
HD duration pre-Tx	<30 days	<8 weeks	>8 weeks
MELD	37	35	34
% needing post-Tx HD	89	79	13
Median duration of post-Tx HD (days)	9	10.5	0
Median length of stay (days)	25	47	25
1-year patient survival	66%	64%	88%

The patient will be considered for a Liver Transplant alone unless we have evidence HRS is reached an irreversible stage by means of Kidney biopsy showing >30% of interstitial fibrosis and/or > 30% of glomerulosclerosis, or dialysis for longer than 8-12 weeks. Should we document one or more of these findings then the patient will be considered for a combined Liver and Kidney

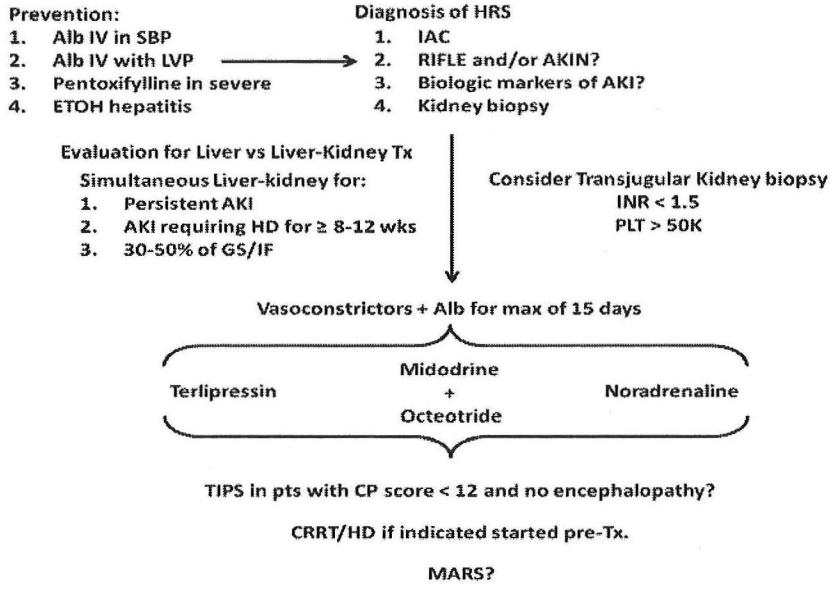
transplantation. The patient that receives a Liver Transplant alone will receive careful monitoring of the kidney function to determine if in the long term the patient develops CKD progressing to ESRD justifying a kidney transplant after the liver transplantation. The kidney could come from the cadaveric donor pool or from a living related or unrelated kidney donor pool. A combined liver and kidney transplant has the advantage of the liver protecting the kidney by means of multiple immunologic mechanisms that are not the focus of this discussion, from antibody-mediated or cellular-mediated rejection. However, in the situation of a kidney after a liver transplantation the liver and the kidney are coming from different donors and that liver is not going to have the immunologic advantages of protecting the kidney from antibody or cellular mediated rejection as in the combined liver and kidney transplants. Kidney survival in combined Liver and Kidney and Kidney after Liver are lower than for Kidney transplant alone but this is mostly due to the fact that Liver transplant patients are sicker and have higher mortality than Kidney recipients so a significant number of Liver transplant patients receiving either a CLKTx or LTA die with a functional renal allograft. Considering the fact that the list of renal transplant candidates is increasing faster than the number of cadaveric or living kidney donors, the allocation of kidneys to CLKTx and/or KALTx need to be done with caution to minimize allocating organs to patients that will not survive and die with a functional kidney allograft that did not contribute to the renal transplant candidates in the waiting list **(Fig. 16)** [49-51].

Fig. 16 Kidney after Liver Transplant vs Combined Liver-Kidney Transplant:



To summarize, my suggested algorithm to evaluate, diagnose and treat HRS patients is shown in **Fig. 17**. First, we should identify any situation where we can prevent the development of HRS. Then, if HRS develops we should initiate an evaluation for possible liver transplant focusing on determining the need for a Liver Tx only vs. Combined Liver and kidney transplant, documentation of duration of renal replacement therapy and consideration for a kidney biopsy. If the patient has AKI requiring dialysis for longer than 8-12 weeks or he gets a kidney biopsy to assess persistence of AKI showing >30% of glomerulosclerosis or interstitial fibrosis, then the patient will be listed for a combined liver and kidney transplantation. In the absence of any one of these indications, the patient will be listed for a liver transplant only. Biologic markers of AKI may show to be of an important role but research is needed. If a kidney biopsy is judged to be needed a transjugular approach

Fig. 17 Suggested approach to the treatment of Hepatorenal syndrome:



is safe and provides adequate samples after correction of coagulopathy. While the transplant work up is initiated the patient can be initiated on vasoconstrictor therapy which can be followed by TIPS if the patient has no contraindication for the procedure, there is no encephalopathy and Child-Pugh score < 12. If the patient develops indications for renal replacement therapy we can consider starting CRRT in anticipation to transplantation or consider MARS.

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