

Renal failure in cirrhosis: prerenal azotemia, hepatorenal syndrome and acute tubular necrosis

Robert W. Schrier¹, Dmitri Shchekochikhin¹ and Pere Ginès^{2,3,4,5}

¹Department of Medicine, University of Colorado Denver, Aurora, CO, USA, ²Hospital Clínic, University of Barcelona, Barcelona, Spain, ³Institut d'Investigació Biomèdica August Pi-Sunyer (IDIBAPS), Barcelona, Spain, ⁴Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain and ⁵Fundación Reina Sofía de Investigación Nefrológica (IRSIN), Barcelona, Spain

Correspondence and offprint requests to: Robert W. Schrier; E-mail: robert.schrier@ucdenver.edu

Keywords: AKIN and RIFLE criteria; acute kidney injury

Recent approaches to predict the prognosis for acute renal failure (ARF) have been proposed. Whether these approaches are applicable to cirrhotic patients is not clear. Recently, acute kidney injury (AKI) was proposed to replace the ARF term [1]. The initial approach to predict the prognosis of the clinical syndrome of acute tubular necrosis (ATN) due to ischemia, toxins or both were the RIFLE criteria [1]. The progressive stages for the RIFLE definition were Risk, Injury, Failure, Loss and End-stage renal disease (ESRD). The stages were based on peak changes in serum creatinine from baseline to 7 days. Risk was defined as ≥ 150 – 200% (1.5- to 2.0-fold), Injury 200–300% (2- to 3-fold) and Failure $\geq 300\%$ (more than 3-fold or serum creatinine ≥ 4.0 mg/dL) in serum creatinine from baseline. Loss was designed as need for dialysis and ESRD indicates dialysis dependence for longer than 4 weeks. Although not clearly stated, this definition is presumably dependent on the knowledge of a stable baseline and assumes that acute glomerulonephritis, post-renal causes (e.g. urinary tract obstruction) and reversible causes (e.g. prerenal azotemia secondary to volume depletion) have been eliminated. Otherwise, predicting prognosis of ARF/AKI from a heterogeneous group of patients with renal dysfunction would be problematic. Earlier research had shown that the faster the rise in serum creatinine, the worse the prognosis in ATN, no doubt due to a hypercatabolic state [2]. The RIFLE criteria, however, has allowed for a more systematic approach which is useful in epidemiological and research studies [3]. A limitation to RIFLE is that in the majority of patients with cirrhosis and infections, ARF/AKI is already present at the time of hospital admission [4], this makes it difficult to define ARF/AKI based on a baseline serum creatinine.

The following approach to predict prognosis in ARF/AKI patients was named AKIN as proposed by the Acute Kidney Injury Network (AKIN) [5]. The AKIN approach used the Risk, Injury and Failure stages of RIFLE and designated them as Stage I, II and III, respectively, to refer to the same increases in serum creatinine concentration from baseline. The peak changes in serum

creatinine concentration within 48 h were designated as AKI classification rather than the 7 days in RIFLE. The Loss and ESRD of the RIFLE definition were excluded because they were considered outcomes rather than predictors. AKIN also designated serum creatinine rises from baseline of ≥ 0.3 mg/dL as Stage I. This decision was based on epidemiological results which indicated that increases in serum creatinine of ≥ 0.3 mg/dL in patients with ARF/AKI are associated with increased mortality [6]. AKIN criteria stated that adequate volume repletion had excluded reversible prerenal azotemia before applying the AKIN criteria. Post-renal azotemia and glomerulonephritis were also to be excluded. As with RIFLE, the AKIN criteria have been shown in epidemiological studies to be associated with increased mortality in ARF/AKI [7]. Decreased urine output criteria also have been proposed in both RIFLE and AKIN to predict survival in ARF/AKI. However, since $\geq 50\%$ of ARF/AKI patients are non-oliguric, i.e. >500 mL/24 h, these criteria are less helpful than the increase in serum creatinine criteria [3, 8]. It should also be noted that RIFLE and AKIN were developed to predict outcome of patients in the intensive care unit with ARF/AKI.

On this background, the question has arisen whether the AKIN criteria can be used for renal dysfunction in patients with cirrhosis. It must first be acknowledged that with ATN, the primary organ injured is the kidney even when associated with sepsis or hypotension, whereas with cirrhosis, the initial organ dysfunction occurs in the liver with secondary renal dysfunction. Thus, advanced renal dysfunction in cirrhotic patients is known as hepatorenal syndrome (HRS). The pathophysiology of cirrhosis involves portal hypertension leading to splanchnic arterial vasodilatation. The resultant primary systemic arterial vasodilatation unloads the arterial stretch receptors in the carotid sinus and aortic arch. This baroreceptor response then triggers the compensatory activation of the neurohumoral axis with stimulation of the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system (SNS) and arginine vasopressin (AVP) (Figure 1) [9]. Stimulation of the RAAS, SNS and AVP contributes to

maintenance of blood pressure by increasing systemic vascular resistance along with the secondary increase in cardiac output. While this compensatory neurohumoral activation attenuates any hypotension secondary to arterial vasodilatation, renal vasoconstriction with sodium and water retention also occurs. This resultant diminished renal function is, however, of a functional nature and thus should not be considered ATN. From an epidemiology standpoint, renal dysfunction can occur with advanced liver diseases independent of the etiology [9].

However, the resultant renal vasoconstriction in cirrhotic patients does predispose to ATN, if a 'second hit' occurs, such as a gastrointestinal hemorrhage, excessive diarrhea with lactulose, sepsis or toxin exposure (e.g. aminoglycosides, non-steroidal anti-inflammatory drugs). With such a second hit leading to ATN, there is evidence of tubular dysfunction as assessed by diminished tubular sodium reabsorption despite a fall in glomerular filtration rate (GFR) [10]. In contrast to ATN, renal

vasoconstriction in the normal kidney, which leads to decreased GFR, is associated with enhanced tubular sodium reabsorption. Thus, in the absence of diuretics, tubular sodium reabsorption increases and results in decreased urinary sodium concentration to <20 mEq/L and fractional sodium excretion to <1.0 . This normal tubular response to renal vasoconstriction and fall in GFR does not occur with ATN. With ATN urinary sodium concentration is increased, fractional sodium excretion exceeds 2.0–3.0 and tubular epithelial cells are present in the urine [10].

The evidence that renal dysfunction in HRS is functional is substantial [9]. Reversal of the renal dysfunction with HRS occurs with liver transplantation in spite of the nephrotoxic effects of immunosuppressive drugs, e.g. calcineurin inhibitors. Renal parenchymal histology in HRS has been shown to be virtually normal, thus not providing an explanation for GFRs <30 mL/min/1.73m² in HRS. To date, there is no evidence that prolonged renal vasoconstriction in HRS leads to ATN in the absence of a

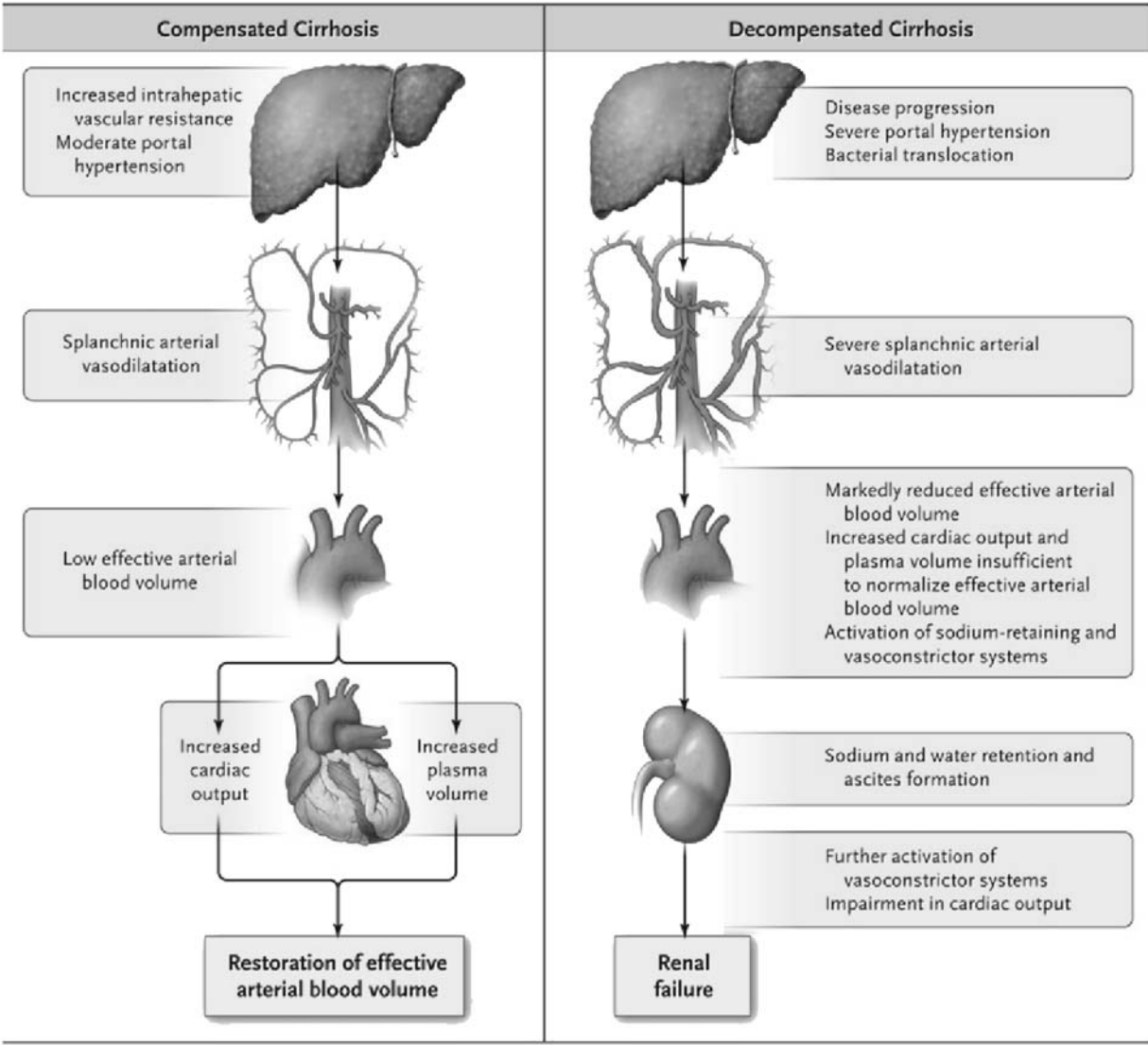


Fig. 1. Pathogenesis of circulatory abnormalities and renal failure in cirrhosis. Used with permission of [9].

secondary ischemic or nephrotoxic insult. Furthermore, there is now evidence for reversal of HRS by treating the arterial underfilling, which occurs secondary to splanchnic vasodilatation. This approach to reverse HRS, other than liver transplantation, involves the combination of terlipressin (V1 AVP agonist) and albumin [11]. In Type I HRS, this therapeutic approach has reversed renal dysfunction over 7–10 days in ~50% of patients.

Although HRS has the characteristics of prerenal azotemia, such as occurring with volume depletion, there are clear differences. The cirrhotic patient with reversible renal dysfunction due to volume depletion secondary to excessive diuresis, hemorrhage or diarrhea should be reversible with volume repletion. The recommended standard approach is to stop diuretics for 2 days and administer 1 g/kg of albumin up to 100 g [9]. This approach should reverse renal dysfunction in the volume-depleted cirrhotic patient, but not in the patient with HRS. The mechanism of the irreversibility of the renal vasoconstriction in HRS with volume expansion is not clear. The more prolonged renal vasoconstriction with HRS may alter the renal vasculature so that reversibility of the vasoconstriction is more difficult than mediated by volume depletion that has occurred over a shorter duration. Alternatively, the intensity of the arterial underfilling may be more important in HRS, which is mainly due to splanchnic arterial vasodilatation without volume loss, than in renal failure due to hypovolemia, which is due to intravascular volume loss.

The prevalence of renal dysfunction in cirrhosis has been divided into Type I HRS (occurs over 2 weeks and has high mortality) and Type 2 HRS (occurs over a much longer period of time and has less mortality) (Table 1). These definitions have established high-risk situations for survival in cirrhosis. Optimally, any new definitions should provide information that potentially enhances the care of cirrhotic patients, since renal dysfunction in cirrhotic patients is already complex. Urinary biomarkers have the potential for being more sensitive than serum creatinine in cirrhosis. Fagundes *et al.* [12] have reported in abstract form that urinary neutrophil gelatinase-associated lipocalin, as well as fractional excretion of sodium, is significantly higher in patients with ATN than HRS. Such results further support the functional nature of HRS compared to ATN in cirrhotic patients.

The use of RIFLE or AKIN criteria for renal insufficiency in cirrhosis has several limitations [13]. Since the functional renal impairment in cirrhosis progresses gradually from compensated to decompensated with ascites to

HRS, the change in serum creatinine from a stable baseline may be difficult in cirrhotic patient without ATN. In the absence of ATN or Type 1 HRS, the functional renal failure of advanced cirrhosis would not be expected to change within 48 h (AKIN) or even 7 days (RIFLE).

Cirrhotic patients have a chronic disease with loss of muscle mass that affects the relationship between serum creatinine and GFR. Unpublished results demonstrated in 318 cirrhotic patients that a serum creatinine of 1.3 mg/dL equated to a mean GFR of 48 mL/min/1.73m², while a serum creatinine of 2.0 mg/dL equaled to 20 mL/min/1.73m². Thus, the relationship between GFR and serum creatinine in a cachectic patient with advanced cirrhosis needs to be considered. In this setting, 'normal' serum creatinine (<1.5 mg/dL) may still indicate substantial renal dysfunction.

In conclusion, much of the renal dysfunction in cirrhosis is functional which occurs secondary to renal vasoconstriction in response to systemic arterial vasodilatation. Because of this renal vasoconstriction, cirrhotic patients are predisposed to developing ATN with a 'second hit', such as gastrointestinal hemorrhage, diarrhea or sepsis. In these critical situations of ATN in cirrhotic patients, prospective studies to assess the value of RIFLE and/or AKIN would be of interest [13]. Currently, the differential diagnosis of ATN from HRS involves the higher fractional excretion of sodium with ATN and sometimes the presence of tubular epithelial cells on urinalysis. In cirrhotic patients, both HRS and prerenal azotemia due to volume depletion exhibit a low fractional excretion of sodium compared to ATN, but only the latter condition reverses with albumin administration and cessation of diuretics.

Acknowledgements. Funding. Some of the studies reported in this editorial comment were performed with the support of grants from the Fondo de Investigación Sanitaria (FIS PI080126 and EC/90077) and Ciber de Enfermedades Hepáticas y Digestivas (CIBEREHD). CIBEREHD is funded by the Instituto de Salud Carlos III, Ministerio de Sanidad, España.

Conflict of interest statement. None declared.

References

- Bellomo R, Ronco C, Kellum JA *et al.* Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; 8: R204–R212.
- Levy MM, Macias WL, Vincent JL *et al.* Early changes in organ function predict eventual survival in severe sepsis. *Crit Care Med* 2005; 33: 2194–2201.
- Cruz DN, Bolgan I, Perazella MA *et al.* North East Italian Prospective Hospital Renal Outcome Survey on Acute Kidney Injury (NeiPHROS-AKI): targeting the problem with the RIFLE Criteria. *Clin J Am Soc Nephrol* 2007; 2: 418–425.
- Martin-Llahi M, Guevara M, Torre A *et al.* Prognostic importance of the cause of renal failure in patients with cirrhosis. *Gastroenterology* 2011; 140: 488–496.
- Mehta RL, Kellum JA, Shah SV *et al.* Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11: R31.
- Lassnigg A, Schmidlin D, Mouhieddine M *et al.* Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic

Table 1. Types of HRS

Type I	Type II
Rapidly progressive	Slower deterioration
Serum creatinine double to >2.5 mg/dL or creatinine clearance <20 mL/min in <2 weeks	Serum creatinine >1.5 mg/dL or creatinine clearance <40 mL/min but decline is slow
Prognosis—80% die in 2 weeks	Most patients die within several weeks
Frequently precipitating events (e.g. spontaneous bacterial peritonitis)	Most frequent cause of therapy-resistant ascites

- surgery: a prospective cohort study. *J Am Soc Nephrol* 2004; 15: 1597–1605.
7. Joannidis M, Metnitz B, Bauer P *et al.* Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med* 2009; 35: 1692–1702.
 8. Anderson RJ, Linas SL, Berns AS *et al.* Nonoliguric acute renal failure. *N Engl J Med* 1977; 296: 1134–1138.
 9. Ginès P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med* 2009; 361: 1279–1290.
 10. Schrier RW. Diagnostic value of urinary sodium, chloride, urea, and flow. *J Am Soc Nephrol* 2011; 22: 1610–1613.
 11. Ginès P, Angeli P, Lenz K *et al.* EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; 53: 397–417.
 12. Fagundes C, Pepin MN, Guevara M *et al.* Evaluation of four different urinary biomarkers in the assessment of renal failure in cirrhosis. Role for urinary neutrophil gelatinase associated lipocalin. *Hepatology* 2011; 54: 1234A.
 13. Wong F, Nadim MK, Kellum JA *et al.* Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut* 2011; 60: 702–709.
- Received for publication: 19.12.2011; Accepted in revised form: 10.2.2012

Nephrol Dial Transplant (2012) 27: 2628–2633

doi: 10.1093/ndt/gfs077

Advance Access publication 25 April 2012

Impact of oral calcium on mortality of dialysis patients—an underestimated risk?

Juergen Bommer^{1,2}, Markus Ketteler³ and Eberhard Ritz⁴

¹University Heidelberg, Heidelberg, Germany, ²Dialysis Center Heidelberg, Heidelberg, Germany, ³Division of Nephrology, Klinikum Coburg GmbH, Coburg, Germany and ⁴Department of Nephrology, University Heidelberg, Heidelberg, Germany

Correspondence and offprint requests to: Juergen Bommer; E-mail: juergen_bommer@t-online.de

Keywords: calcification; calcium; haemodialysis; phosphate; phosphate binder

Phosphate is an accepted trigger and promoter of soft tissue calcification. Today, oral calcium-containing phosphate binders are still frequently administered to reduce hyperphosphataemia in patients with reduced renal function. There is, however, increasing evidence that a positive calcium balance and elevated serum calcium concentrations may aggravate soft tissue calcification. Some recent controlled [1, 2] trials as well as recent unpublished observational evidence from Dialysis Outcome and Practice Pattern Study (DOPPS) point to increased mortality in renal patients treated with calcium-containing P binders. Unfortunately, each of these studies has some methodological limitations. Nevertheless, a recent meta-analysis documented an increased risk of myocardial infarction and stroke even in patients without kidney disease when treated with calcium supplements [3].

Chronic kidney disease and calciuria

In the 1950s, several studies had documented that urinary calcium excretion is strikingly reduced even in early stages of chronic kidney disease (CKD) at a glomerular filtration rate of <80 mL/min [4]. This is one major and underestimated factor that contributes to the elevated risk of a positive calcium balance when CKD patients are exposed to

high calcium loads. These early findings have recently been confirmed and extended to CKD Stages 4 and 5 in patients whose calcium excretion was reduced to <50 mg/24 h [5]. Obviously in anuric patients with end-stage renal disease, calcium excretion is completely absent; in such anuric dialysis patients, the calcium load can only be lowered by using a low dialysate calcium concentration and/or a high ultrafiltration volume during dialysis.

The need for phosphate binders

Even though in CKD 1–3 serum phosphate concentrations usually still remain within the normal range, although at the expense of increased fibroblast growth factor (FGF) 23 and intact parathyroid hormone (iPTH) [6], it has nevertheless become obvious that even in the presence of moderately reduced renal function, phosphate plays a crucial role in the development of soft tissue calcification [7]. The propensity to calcify soft tissues, specifically vascular tissue, is accelerated by a positive phosphate balance. Importantly, however, in addition, it is promoted by additional local and systemic factors including calcification inducers and inhibitors, local apoptosis, matrix degradation etc. [8, 9]. This may explain the observation that the prevalence of vascular calcification is increased dramatically even prior to end-stage kidney disease [10].