Hyponatremia in Cirrhosis 149
Helbert Rondon-Berrios and Juan Carlos Q. Velez

Hyponatremia is the most common electrolyte disorder encountered in clinical practice, and it is a common complication of cirrhosis reflecting an increase in nonosmotic secretion of arginine vasopressin as a result of the circulatory dysfunction that is characteristic of advanced liver disease. Hyponatremia in cirrhosis has been associated with poor clinical outcomes including increased risk of morbidity and mortality, poor quality of life, and heightened health care utilization. Despite this, the treatment of hyponatremia in cirrhosis remains challenging as conventional therapies such as fluid restriction are frequently ineffective. In this review, we discuss the epidemiology, clinical outcomes, pathogenesis, etiology, evaluation, and management of hyponatremia in cirrhosis.

Hepatorenal Syndrome: Pathophysiology 165
Timea Csak and David Bernstein

Hepatorenal syndrome (HRS) is defined as a functional renal failure without major histologic changes in individuals with severe liver disease and it is associated with a high mortality rate. Renal hypoperfusion due to marked vasoconstriction as a result of complex circulatory dysfunction has been suggested to be the cornerstone of HRS. Splanchnic and peripheral arterial vasodilation and cirrhotic cardiomyopathy result in effective arterial hypovolemia and compensatory activation of vasoconstrictor mechanisms. The efficacy of current therapeutic strategies targeting this circulatory dysfunction is limited. Increasing evidence suggests a substantial role of systemic inflammation in HRS via either vascular or direct renal effects. Here we summarize the current understanding of HRS pathophysiology.

Hepatorenal Syndrome: Definitions, Diagnosis, and Management 181
Sebastiano Buccheri and Ben L. Da

Hepatorenal syndrome (HRS) is a hemodynamically driven process mediated by renal dysregulation and inflammatory response. Albumin, antibiotics, and β-blockers are among therapies that have been studied in HRS prevention. There are no Food and Drug Administration-approved treatments for HRS although multiple liver societies have recommended terlipressin as first-line pharmacotherapy. Renal replacement therapy is the primary modality used to bridge to definitive therapy with orthotopic liver transplant or simultaneous liver-kidney transplant. Advances in our understanding of HRS pathophysiology and emerging therapeutic modalities are needed to change outcomes for this vulnerable population.
Glomerular Disease in Liver Disease
Purva Sharma and Medha Airy

Glomerular diseases are an important cause of kidney disease in patients with liver disease. Although kidney involvement due to tubular or vascular disease is more common, glomerular diseases became more prevalent as hepatitis infections increased and then subsequently decreased with the widespread availability of hepatitis A and B vaccines and the development of effective antiviral treatments for hepatitis B and C. In this review, we discuss the common glomerular pathologies that are seen in patients with liver disease and the current treatment options available to them.

The Interplay Between Nonalcoholic Fatty Liver Disease and Kidney Disease
Emily Truong and Mazen Noureddin

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, involving approximately 25% of the general population and increasing in prevalence in patient populations afflicted with metabolic syndrome and type 2 diabetes. This article discusses the complex interplay between NAFLD and chronic kidney disease (CKD), as well as the underlying pathogenesis and mechanisms through which NAFLD and CKD are linked. Exploration of these sophisticated relationships and causative factors is essential to accurately assessing kidney function in patients with NAFLD, recommending pharmacologic treatment of disease, and identifying favorable avenues for future investigation.

Polycystic Kidney/Liver Disease
Rebecca Roediger, Douglas Dieterich, Pramodh Chanumolu, and Priya Deshpande

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder that leads to chronic kidney disease and end-stage kidney disease (ESKD). Polycystic liver disease (PCLD) is the most common extrarenal manifestation of ADPKD. Though isolated PCLD and PCLD due to ADPKD are genetically distinct, they follow a similar clinical course of hepatomegaly from multiple cysts with preserved liver function. Tolvaptan use in ADPKD can slow down the deterioration of renal function and growth of cysts. Somatostatin analogs can slow the growth of polycystic livers but the effect is short-lived. The only curative therapy for PCLD is liver transplantation. Renal transplantation can significantly improve survival in patients with ESKD due to ADPKD.

Kidney Replacement Therapy in Patients with Acute Liver Failure and End-Stage Cirrhosis Awaiting Liver Transplantation
Karthik Kovvuru and Juan Carlos Q. Velez

Providing dialysis to patients with liver failure is challenging because of their tenuous hemodynamics and refractory ascites. With better machinery and increased availability, continuous kidney replacement therapy has been successfully delivered to acutely ill patients in liver failure over the past few decades. Intermittent hemodialysis continues to remain the modality of choice outside the intensive care unit and on occasion needs to be
complemented with paracentesis. Peritoneal dialysis has not been widely used, but recent literature shows promising outcomes barring for publication bias. Albumin dialysis could be a lifesaving procedure for a carefully selected subgroup of patients with liver failure.

**Peritransplant Renal Dysfunction in Liver Transplant Candidates**

*Rajiv Heda, Alexander J. Kovalic, and Sanjaya K. Satapathy*

Renal function is intricately tied to Model for End-Stage Liver Disease score and overall prognosis among patients with cirrhosis. The estimation of glomerular filtration rate (GFR) and etiology of renal impairment are even more magnified among cirrhotic patients in the period surrounding liver transplantation. Novel biomarkers including cystatin C and urinary neutrophil gelatinase-associated lipocalin have been demonstrated to more accurately assess renal dysfunction and aid in the diagnosis of competing etiologies. Accurately identifying the severity and chronicity of renal dysfunction among transplant candidates is an imperative component with respect to stratifying patients toward simultaneous liver-kidney transplantation versus liver transplantation alone.

**Pros and Cons of the Safety Net Rule for Prioritization of Liver Transplant Recipients Who Receive Liver Alone Transplant but Develop End-Stage Renal Disease**

*Mark W. Russo and Vincent Casingal*

The number of patients presenting with cirrhosis with kidney injury and the potential need for SLKT is increasing. In 2017, standardized criteria were implemented to identify candidates for SLKT as well as criteria for prioritizing LTA recipients for kidney transplant if they developed kidney failure, which is referred to as the ‘safety net rule.’ Goal of the safety net rule is to provide a pathway that provides increased priority to LTA recipients with renal failure who may have previously undergone SLKT. This article reviews the pros and cons of the safety net rule for liver transplant recipients who develop ESRD.

**Kidney Allocation Issues in Liver Transplantation Candidates with Chronic Kidney Disease and Severe Kidney Liver Injury**

*Daniel Lia and Elliot I. Grodstein*

The number of liver transplant candidates with concomitant renal disease has been steadily rising since the implementation of MELD-based allocation in 2002. Consequently, the number of simultaneous liver-kidney (SLK) transplants being performed each year has also increased. However, the establishment of well-defined criteria for when to choose SLK over liver transplant alone has lagged behind. The lack of clear guidelines has worsened an already large shortage of transplantable kidneys. This article further explores the rationale for and outlines the implementation of the SLK allocation policy.
The Use of Hepatitis C Virus–Positive Organs in Hepatitis C Virus–Negative Recipients

Christian Kuntzen and Zohaib Bagha

The use of hepatitis C virus (HCV) -positive organs in HCV-negative recipients with posttransplant antiviral treatment has increasingly been studied since the introduction of new direct-acting antivirals. This article reviews existing experience in liver and kidney transplant. Fifteen studies with 218 HCV D+/R-/C0 liver transplants, with 182 from viremic donors, show a sustained viral response for 12 weeks (SVR12) rate of 99.5%. Nine studies involving 204 HCV donor-positive recipient-negative kidney transplant recipients had an SVR12 rate of 99.5%. Complications are infrequent. Pre-emptive treatment in kidney transplant of for only 4 weeks or even 4 days showed surprising success rates.

Simultaneous Liver–Kidney Transplantation

Gayatri Nair and Vinay Nair

End-stage kidney disease (ESKD) after liver transplantation is associated with high morbidity and mortality. This increase in mortality can be offset by performing a kidney transplant at the time of the liver transplant in select cases. Accordingly, Margreiter and colleague’s performed the first simultaneous liver–kidney (SLK) transplant in 1983. The number of SLK transplants has increased by more than 300% since then. In 1990%, 1.7% of all liver transplants in the United States were SLK transplants which increased to 9.9% by 2016. This steep increase was likely due to the implementation of the model of end-stage liver disease (MELD) scoring system in 2002, which is heavily weighted by serum creatinine.

Chronic Kidney Disease After Liver Transplantation

Ramon O. Minjares, Paul Martin, and Andres F. Carrion

Improved survival after liver transplantation has led to an aging cohort of recipients at risk of renal dysfunction. The etiology of renal dysfunction is typically multifactorial; calcineurin inhibitors nephrotoxicity, pretransplant renal dysfunction, and perioperative acute kidney injury are important risk factors. Metabolic complications such as hypertension, diabetes mellitus, and metabolic-associated fatty liver disease also contribute to the development of renal disease. Most LT recipients will eventually develop some degree of renal dysfunction. Criteria to select candidates for simultaneous liver and kidney transplantation have been established. Both delayed introduction of CNIs and renal-sparing immuno-suppressive regimens may reduce progression of renal dysfunction.