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Position Paper

Position paper on liver and kidney diseases from the Italian Association for the Study of Liver (AISF), in collaboration with the Italian Society of Nephrology (SIN)☆

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ABSTRACT

Liver and kidney are strictly connected in a reciprocal manner, in both the physiological and pathological condition. The Italian Association for the Study of Liver, in collaboration with the Italian Society of Nephrology, with this position paper aims to provide an up-to-date overview on the principal relationships between these two important organs.

A panel of well-recognized international expert hepatologists and nephrologists identified five relevant topics: 1) The diagnosis of kidney damage in patients with chronic liver disease; 2) Acute kidney injury in liver cirrhosis; 3) Association between chronic liver disease and chronic kidney disease; 4) Kidney damage according to different etiology of liver disease; 5) Polycystic kidney and liver disease. The discussion process started with a review of the literature relating to each of the five major topics and clinical questions and related statements were subsequently formulated. The quality of evidence and strength of recommendations were graded according to the GRADE system.

The statements presented here highlight the importance of strong collaboration between hepatologists and nephrologists for the management of critically ill patients, such as those with combined liver and kidney impairment.

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1. Introduction

Liver and kidney, as is well known, are strictly connected in a reciprocal manner, in both the physiological and pathological condition.

The aim of this position paper, conceived as an initiative of the Italian Association for the Study of Liver (AISF), in collaboration with the Italian Society of Nephrology (SIN), is to provide an up-to-date overview on the functional, metabolic and pathological relationships between liver and kidney. Both hepatic diseases involving renal function and renal diseases involving hepatic function are discussed, also including the topic of organ transplantation as treatment for advanced forms of both hepatic and renal disease.

In order to provide the clinical community with an updated document, the AISF and SIN appointed a panel of well-recognized international experts to the scientific board. The members of the Permanent Commission for Liver Transplantation (CPT) of AISF were identified as the experts for this position paper, with the support of an external hepatologist. SIN included in the expert panel nephrologists skilled in the argument.

The scientific board of experts identified 5 relevant topics: 1) The diagnosis of kidney damage in patients with chronic liver disease; 2) Acute kidney injury in liver cirrhosis; 3) Association between chronic liver disease and chronic kidney disease; 4) Kidney damage according to different etiology of liver disease; 5) Polycystic kidney and liver disease. Subsequently, literature data search relating to each of the five major topics was conducted by ad hoc subcommittees of experts. Forty-seven clinical questions and related statements were formulated. The quality of the evidence and strength of recommendations were graded according to the GRADE system [1]. The strength of the evidence was classified in four levels: high (A), moderate (B), low (C), and very low (D) quality evidence, while the recommendations were divided into strong (1) and weak (2). Where formal evidence was not available and statements were based on expert opinion, the term “ungraded” was used. All panel members revised the initial draft, so the final version represents the consensus of the entire working group.

AISF and SIN are confident that this document will be easily accessible to the hepatological and nephrological community and that it can represent the starting point for collaborative studies and future scientific initiatives in the field between the two associations.

2. The diagnosis of kidney damage in patients with chronic liver disease

2.1. Renal function in chronic liver disease

The relationship between the liver and kidney are reciprocal at different levels but, in the case of compensated chronic liver damage, the main actors are hepatitis viruses, e.g. hepatitis A (HAV), B (HBV), C (HCV) and E (HEV). Among these, HBV and HCV affect nearly 7% of the world’s population and renal failure is the most frequent extra-hepatic complication. The two more frequent renal diseases associated with chronic HBV infection are membranous nephropathy with its classical symptoms of nephrotic syndrome or asymptomatic proteinuria and polyarteritis nodosa, a necrotizing vasculitis of small and medium-sized vessels; kidney involvement, very frequent in the pediatric population, consists of renal artery vasculitis leading to proteinuria and hypertension [2].

More clearly depicted is renal involvement in HCV infection which, mediated by the intervention of different mechanisms, either directly related to kidney infection or mediated by the host’s immune response, is associated with a wide spectrum of glomerular diseases. The most frequently observed is cryoglobulinemic glomerulonephritis secondary to type II mixed cryoglobulinemia [3,4].

Patients with HCV-related nephropathy may be totally asymptomatic with occult urinary abnormalities or clinically evident with multiform manifestations of cryoglobulinemic vasculitis. Thus, pictures ranging from microscopic hematuria to severe proteinuria, associated with mild to severe impairment of renal function from 2% to 31% have been reported [5].

In parallel with the most frequent type of HCV nephropathy, diagnosis relies on the biochemical findings of typical markers of mixed cryoglobulinemia: rheumatoid factor positivity, consumption of C4 complement, positive HCV markers and cryocrit. Renal histology observed in HCV related cryoglobulinemic glomerulonephritis secondary to type II mixed cryoglobulinemia typically shows the duplication and interposition by mesangial cells of the glomerular basement membrane, mesangial proliferation and endoluminal hyaline pseudo thrombi. Immunofluorescence microscopy may reveal C3, IgM and IgG depositions on the capillary wall and mesangium. Intraluminal and subendothelial deposits may show a fibrillary pattern under electron microscopy, likely representing cryoglobulin deposition [6].

2.2. Renal function in liver cirrhosis

Renal dysfunction is a severe and highly prevalent complication of advanced cirrhosis related to two main pathophysiological mechanisms: splanchnic arterial vasodilation and systemic inflammation [7–9]. Renal dysfunction significantly affects treatment strategies and natural history of the disease as well as allocation policies in a transplant setting. The accurate assessment of renal function is therefore of paramount importance in patients with liver cirrhosis. Two main types of kidney dysfunction are described in cirrhotic patients: chronic kidney disease (CKD) and acute kidney injury (AKI). According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines CKD is defined by the presence of kidney structure alterations (urinary abnormalities, histological and/or ultrasound signs of renal damage) or function (GFR $<$ 60 mL/min/1.73 m^2) for at least 3 months [10]. Among different types of CKD, type 2 Hepatorenal Syndrome (HRS) is specifically observed in cirrhosis as a slowly progressive renal failure [11]. The hemodynamic dysfunctional nature of Type-2 HRS is confirmed by its reversibility with liver transplantation (LT) [12]. The most challenging form of kidney dysfunction in liver cirrhosis is AKI, occurring in 20–30% of hospitalized cirrhotics and with a very high 3-month probability of mortality ranging from 28% to 47% [13]. AKI in cirrhosis will be extensively discussed in Section 2.

2.2.1. Biomarkers of renal function in liver cirrhosis

Overall, the best index of kidney function is the glomerular filtration rate (GFR), namely the volume of fluid filtered from the kidney glomeruli into the Bowman’s capsule per minute. Usually, GFR per se is used to define CKD stages and AKI. Although the gold standard for the measurement of GFR is the clearance of exogenous filtration markers (inulin, iohexol, or radioactive markers), nevertheless they are not widely used in clinical practice due to concerns over costs, time consumed and not repeatable measurements. Thus, several surrogate markers of GFR have been developed. The most common are serum creatinine (sCr), blood urea nitrogen (BUN), and cystatin C (CystC). However, if sCr has several limitations in healthy people due to influence of age, gender, ethnicity, body weight and muscle mass, accuracy is even lower when measured in patients with liver cirrhosis. Indeed, liver cirrhosis conditions such as reduced production of creatinine due to sarcopenia, increased tubular secretion of creatinine, interference of elevated bilirubin levels and use of diuretics interfere with sCr assays, causing an overestimation of sCr in patients with

cirrhosis [14]. The equations suggested to calculate estimated GFR (eGFR) in the general population [Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) etc], suffered the same limitations in cirrhotic patients when sCr was included

CystC is a 13-kDa basic protein recently used in the general population as a biomarker of kidney function. Specific data in cirrhotic patients were derived by De Souza et al. who compared different GFR equations (MDRD-4, MDRD-6, CKD-EPI-sCr, CKD-EPI-CystC) in 202 cirrhotic patients candidates for LT, using inulin clearance as a reference. CystC-based equations resulted as having a better performance than sCr-based ones. Additionally, CKD-EPI-CystC equation showed the best performance whatever the ascites severity and in the presence of significant renal dysfunction (GFR $<$ 60 mL/min/1.73 m^2). Thus, CystC-based equations, especially CKD-EPI-CystC, may be recommended to evaluate renal function in cirrhotic patients [15].

2.2.2. Urinary Biomarkers of renal function in liver cirrhosis

Despite the lack of a standard simple marker of kidney injury in liver cirrhosis, differentiating acute tubular necrosis (ATN) and HRS-AKI, the two main entities of AKI, is of paramount importance for treatment choice and prognostic outcome. Currently, diagnosis is made on clinical grounds sometimes with some classical urine biomarkers, urine sodium concentration or fractional excretion of sodium. Recently, neutrophil gelatinase–associated lipocalin (NGAL) and interleukin (IL)-18 have been investigated in clinical studies as new biomarkers to differentiate ATN and HRS-AKI.

NGAL is a 25 kD protein produced by several cells and tissues. Several studies performed on patients with cirrhosis demonstrated that NGAL has good discrimination ability in differentiating ATN from the other types of AKI as it may be a good predictive marker of AKI and mortality [16]. Recently, Huelin et al. investigated in a prospective study the accuracy of several biomarkers in differential diagnosis of AKI and in predicting kidney outcome and patient survival in 320 consecutive cases of AKI in patients hospitalized for decompensated cirrhosis. For this purpose, NGAL, monomeric NGAL, IL-18 and standard biomarkers were measured at diagnosis and on days 3, 7 and 14. Among all biomarkers, urinary NGAL measured on day 3 exhibited the greatest accuracy for differential diagnosis between ATN and other types of AKI (AUC 0.87; 95% confidence interval, 0.78–0.95). Moreover, NGAL resulted independently associated with progression of AKI during hospitalization and with 28-day mortality [17].

Infections and systemic inflammation, the hallmark of acute-on-chronic liver failure (ACLF) causing the most represented AKI clinical scenario in liver cirrhosis, may interfere with NGAL measurements and thus hamper the potential diagnostic and prognostic value of this biomarker [18].

IL-18 is a 22 kD proinflammatory cytokine recognized as a mediator of renal ischemia–reperfusion injury and associated AKI. It has been demonstrated that this biomarker shows lower levels in patients with hypovolemia-induced AKI and higher levels in ATN-AKI. A recent meta-analysis reported the usefulness and high accuracy of urinary NGAL and IL-18 in differential diagnosis of several causes of AKI in liver cirrhosis [19].

The Kidney Injury Molecule-1 (KIM-1) is a transmembrane protein that is not expressed in normal kidneys. Its levels increase in the urine upon kidney injury and it has been used in recent years as a sensitive marker for the early diagnosis of glomerular injury [20]. However, the ability to differentiate AKI in patients with cirrhosis does not achieve high accuracy. Limited data exist on the ability of other two biomarkers (urinary L-FABP and urinary CystC) to predict progression of AKI and death in cirrhotic patients with AKI [21]. Thus, besides the promising performance of NGAL and IL-18 in differentiating the different forms of AKI, further studies are needed to elucidate their clinical utility.

2.3. Kidney diseases

2.3.1. Renal fibrosis

Renal fibrosis is a pathological hallmark of progressive renal damage due to extensive fibroblast activation. The extracellular matrix produced by activated fibroblasts leads to destruction of renal parenchyma and progressive loss of kidney function. Renal biopsy is considered the gold standard for evaluation of renal fibrosis, although its invasiveness prevents a wide application in clinical practice. The presence of abnormal coagulation and technical difficulties makes it even more difficult to be applied in the context of liver cirrhosis. Searching for an applicable non-invasive method for clinical diagnosis, magnetic resonance imaging (MRI) gadolinium-free techniques emerged as a promising method for non-invasive and longitudinal evaluation of renal fibrosis. Zao et al. assessed the performance in detecting renal fibrosis of diffusion-weighted MRI in 40 CKD patients (25 of whom had renal histology) and 30 healthy volunteers. Mean renal medullary and cortical apparent diffusion coefficient values were investigated in respect to standard biochemical renal markers and renal histopathological scores. The significant correlation found between cortical and medullary apparent diffusion coefficient with histopathological fibrosis score suggests the potential usefulness of MRI as non-invasive imaging method of renal fibrosis [22].

Another method explored in this setting is Magnetic Resonance Elastography (MRE) a novel MRI-based technique able to capture direct visualization of shear waves propagation in organ tissues. Consistent data in hepatological settings showed that this technique is accurate for liver fibrosis staging [23] and data explored in a kidney transplant (KT) setting indicates that MRE may have the potential to detect and stage renal fibrosis [24].

However, renal stiffness interference on renal flow requires further studies addressing reproducibility and correction factors.

2.3.2. Kidney disease associated with liver disease

Kidney disease occurs in 20%–25% of patients with liver disease and the associated kidney lesions vary widely, ranging from glomerulonephritis typically described in viral and alcoholic hepatitis, to acute or chronic tubulointerstitial injury [25–27]. Among the systemic diseases associated with secondary immunoglobulin (Ig) A nephropathy, liver cirrhosis is the most commonly described. Glomerulonephritis due to liver cirrhosis is characterized by IgA deposits, other immunoglobulins and complements. This is the most commonly seen picture in alcoholic cirrhosis but similar ones are described in viral hepatitis.

Most of these data came from autopsy studies showing mild mesangial IgA deposits in 65% of patients with cirrhosis [28]. Abnormal coagulation and thrombocytopenia as well as kidney fibrosis and/or large volume ascites, makes percutaneous kidney biopsy difficult in most cirrhotic patients. Transjugular kidney biopsy could be an alternative with some limitations [29].

More recently, Hemminger et al. reported on renal lesions in native kidney biopsies from 118 patients with liver cirrhosis evaluated during a 13-year period. While 56% of cases were identified as having mild IgA deposits in the kidney, more strikingly, 6 out of 9 patients with intense immune deposits were diagnosed as having an infection associated glomerulonephritis opening an issue of the importance of AKI associated ACLF in view of the high prevalence of infections as triggering factor for ACLF [30].

The high prevalence and ominous prognosis of AKI in patients with cirrhosis, together with the high impact in addressing allocation policies in the setting of transplantation, makes it a challenge to discover whether AKI has a structural component in addition

to its functional nature. More striking is the issue of whether AKI could proceed to CKD in cirrhosis. In candidates for LT, Maiwall et al. recently addressed in a prospective cohort study the incidence and risk factors for development of CKD in patients with cirrhosis developing AKI. Among 818 cirrhotic patients, overall 36%, 27% and 61% had an AKI episode at enrollment, in their previous history and new AKI during follow-up, respectively. CKD developed in 33% of patients and higher Model for End-Stage Liver Disease (MELD), CystC levels and number and stage of AKI episodes were found to predict CKD development. The development of CKD in the AKI setting was confirmed to be associated with worse outcomes and an independent predictor of mortality [31]. An interesting finding in this study was the availability of adequate renal biopsies in 55 patients, revealing the presence of structural kidney changes in all the patients, the majority of whom had acute or chronic tubulointerstitial injury; in the acute forms, a sizeable proportion of patients had alcohol-related liver disease.

2.4. Use of contrast media

The occurrence of AKI resulting from the intravascular administration of contrast media (CM), namely contrast-induced nephropathy (CIN) has been described since the 1950s followed by large series in the 1980s, mainly in the setting of coronary angiography. The incidence of CIN in the general population has been reported to range from 0% to 24% due to differences in definition, background risk factors, type and dose of contrast medium used, and the frequency of other coexisting potential causes of acute renal failure [32]. Preexisting CKD and diabetes are the strongest risk factors [33]. Overall, the medical community until recently widely agreed that CM is capable of causing AKI. This concept had been supported by the experimental literature on contrast associated nephrotoxicity [34].

Criticisms of the classical position regarded methodological limitations in the initial studies, which were lacking control groups and, in most instances, not adjusted for frequently concomitant AKI risk factors (prevalent CKD). Thus, large propensity score–adjusted studies on intravenous CIN were set up. A retrospective propensity score–adjusted analysis was performed on ATN by McDonald et al. with the aim of evaluating the risk of AKI in a large cohort of patients exposed to contrast-enhanced computed tomography (CECT) or unenhanced computed tomography (CT). AKI risk resulted not significantly different between contrast and non-contrast groups with an incidence similar for each eGFR cohort ($\geq$90 mL/min: 1.2%–1.3%; 60–89 mL/min: 2.1% vs. 2.0%; 30–59 mL/min: 5.8% vs. 6.2%; and $<$30 mL/min: 14% vs. 14%, respectively) [35]. Davenport et al., through several propensity score–adjusted cohort analysis associated with risk stratification of CIN in more than 17,000 patients who again underwent CECT or unenhanced CT, identified in an eGFR of less than $<$30 mL/min an independent risk factor for post-CT AKI (odds ratio, 3.96 [95% CI, 1.29–12.21]; $p = 0.016$). Among the historical risk factors, diabetes, age more than 60 years, hypertension, loop diuretic use, hydrochlorothiazide use, and cardiovascular disease were evaluated for modulation of CIN risk [36,37].

If the results from these studies led to the conclusion that rates of AKI from intravenous CM are in general overstated, conflicts remain in patients with moderate to severe CKD due to the persistence, even in the propensity score analysis, of many confounders such as prophylactic strategies, peri-scan nephrotoxic medications, instability of sCr. Due to these limitations, and the coexistence of some risk factors, for example CKD and diabetes, physicians should take into consideration each patient's specific risk factors for CIN and weigh this against the clinical benefit of performing CECT.

This could be the case for patients with chronic liver disease (CLD). Indeed, patients with liver cirrhosis are a population often requiring contrast medium enhanced CT for several reasons: diagnosis and monitoring of hepatocellular carcinoma (HCC), differential diagnosis between intracranial hemorrhage and encephalopathy, vascular architecture definition and oncological screening before LT etc.

As regards prophylactic measures, research on the prevention of contrast-associated AKI has focused principally on the use of renal replacement therapies, pharmaceutical agents, and intravenous crystalloid. The benefits of prophylactic measures have not been proved; periprocedural intravenous crystalloid infusion remains the primary intervention to mitigate risk. Thus, in order to not deprive patients of important diagnostic information, efforts are required to apply preventive strategies This generally accepted measure intersects the hemodynamic imbalance of fluids typically observed in decompensated cirrhosis; this means that the administration of isotonic fluids could led to impairment of the hydrodynamic balance of cirrhosis. Furthermore, in cirrhotic patients, the presence of ascites had been found to be a significant risk factor for the development of CIN in two retrospective studies. An analysis by the Rochester group in 2009, showed, among 216 patients with cirrhosis who underwent CT with intravenous contrast, that ascites was a significant risk factor for the development of CIN ($p = 0.0009$, OR 3.38, 95% CI 1.55–7.34) in a population in whom CIN was diagnosed in 25% of cases [38]. Filomia et al. evaluated the occurrence and predisposing factors of AKI in 249 cirrhotic patients undergoing CECT. AKI was diagnosed in 8.8% vs. 3% in the CECT and control groups, respectively ($p = 0.01$). At multivariate logistic regression analysis, the presence of ascites (OR: 2.796, 95% CI: 1.109–7.052; $p = 0.029$), female sex (OR: 0.192, 95% CI: 0.073–0.510; $p = 0.001$), and hyperazotemia (OR: 1.018, 95% CI: 1.001–1.037; $p = 0.043$) correlated with CIN-AKI development [39].

Searching for a specific measure to prevent CIN in patients with cirrhosis, Choi et al. retrospectively evaluated the effect of prophylactic intravenous albumin infusion in 81 subjects with liver cirrhosis and CKD. Patients either received isotonic sodium bicarbonate solution or albumin. In this series, CIN incidence rate was 3.7% without significant difference between the two prophylactic groups [40]. Overall, the risk of CIN is present in cirrhosis and possibly higher than in the general population. Increased discussion between radiologists and physicians must be encouraged and, in patients at risk of CIN, non-iodinated contrast studies (contrast-enhanced ultrasound or MRI) as well as the use of newer gadolinium-based contrast agents, may be useful to obtain diagnostic information without depriving patients of the benefit of a cure [41].

2.5. Evaluation of renal function in patients with complicated liver cirrhosis

Renal failure is one of the main predictive factors of mortality in cirrhotic patients. Moreover, the grade and duration of kidney damage before LT are predictors of poor outcome in the post-LT period in terms of mortality and CKD [42]. Even more important is a careful evaluation of renal function in the LT setting as creatinine enter the MELD model allocation system, globally used as a tool for prioritization of liver grafts. Thus, careful evaluation of renal function is necessary.

However, neither creatinine serum level measurements nor sCr based equations correctly estimate renal function, especially at low GFR, due to interference of non-GFR determinants frequently present in patients with CLD [15]. In fact, the presence of ascites and use of diuretics, malnutrition, hyperbilirubinemia are demonstrated to interfere with sCr levels, underestimating the grade of kidney dysfunction [43]. Francoz et al. compared GFR equations to true GFR using iohexol clearance in 300 candidates for liver transplantation. Measured GFR (mGFR) was compared to MDRD-4, MDRD-6, and CKD-EPI equations, and MDRD-6 resulted the most

accurate equation at identifying cirrhosis patients with true GFR <30 mL/min/1.73 m^2, namely the critical cut-off usually used as an indication for a combined liver-kidney transplantation [44].

A recent study evaluated the impact of low muscle mass on evaluation of renal function in cirrhosis by comparing creatinine or cystatin C based eGFR measurements with mGFR in 779 cirrhotic patients. The rate of eGFR overestimation was 47% and skeletal muscle mass together with female sex and more advanced liver dysfunction were identified as predictive risk factors [45].

Medical advances in managing end-stage organ disease have led to an increasing demand for multi-organ transplant and introduction of the MELD score in the liver allocation policy in 2002 resulted in a significant increase in the number of simultaneous liver-kidney transplantations (SLKT) in the USA. Thus, the question of a proper assessment of extent of renal failure in patients with liver cirrhosis became more and more critical in view of the impact that this strategy could have on the donor pool. In this direction, two recent studies from the USA and UK tried to develop a model for GFR assessment in liver disease aiming to improve diagnostic accuracy in the low GFR stages.

Asrani et al. developed a model for GFR assessment in liver disease, namely "GRAIL", before and after LT. GRAIL was derived using objective variables (creatinine, blood urea nitrogen, age, gender, race and albumin) and compared to mGFR by iothalamate clearance (n = 12,122, 1985–2015) as well as to CKD-EPI and MDRD-4 and MDRD-6 equations for mGFR < 30 mL/ min/1.73 m^2, resulting more accurate and precise for low GFR. Before LT, GRAIL correctly classified 75% of patients as having mGFR<30 mL/min/1.73 m^2 vs. 36.1% (CKD-EPI), 36.1% (MDRD-4) and 52.8% (MDRD-6) ($p < 0.01$). Therefore, GRAIL may serve as an alternative model to estimate GFR among patients with liver disease before and after LT at low GFR [46].

Kalafateli et al. developed and validated a cirrhosis GFR equation including 469 consecutive patients who had a transplant assessment between 2011 and 2014. The derived "Royal Free cirrhosis GFR formula" showed greater accuracy compared to that of existing formulae. Many of the conditions that interfere with GFR measurement in liver cirrhosis (female sex, sarcopenia, INR, ascites, sodium) were analyzed and weighted in the formula allowing a significantly better accuracy than the existing formulae (89% vs. 27%–75% of estimates being within 30% of true GFR) [47].

Questions

Q1. Are there any specific diagnostic markers of renal involvement in chronic liver disease?

Apart from urinary abnormalities, proteinuria and decline in renal function, no specific urinary, biochemical or morphological renal markers are available for kidney disease associated with CLD (Ungraded).

Comment

Alterations of kidney function are often observed in patients with CLD, and HBV and HCV chronic infection are the most frequent causes. The presence of renal involvement in this setting relies on assessment of the classic CKD diagnostic flow i.e. identifying the cause (glomerular, vascular, tubulointerstitial, cystic or congenital), defining the level of renal function, and assessing the presence of renal damage. The lack of typical diagnostic markers in this setting require thinking about policy and a strict multidisciplinary approach between nephrologists and hepatologists as the sole way to properly address and timely define follow-up and therapies. Studies are needed to identify potential typical histochemical, urinary or biochemical findings in relation to CKD associated CLD.

Q1.2. What are the preferred biochemical measurements of renal function in patients with liver cirrhosis?

In patients with liver cirrhosis, the assessment of renal function is paramount in view of its impact on treatment strategies and prognosis as well as in addressing transplant policies (1A).

Among different GFR equations, CystC-CKD-EPI formula has the better performance in assessing GFR in cirrhotic patients in the presence of significant renal dysfunction (GFR <60 mL/min/1.73 m^2 (1A).

MDRD-6 is the most accurate equation for identifying cirrhotic patients with true GFR <30 mL/min/1.73 and is thus the suggested measure in addressing allocation policies in the setting of combined liver-kidney transplantation (1A).

Comment

Liver cirrhosis is often associated with kidney impairment. The functional and dynamic nature of this association and the presence of many cirrhotic factors interfering with eGFR measurements makes it a clinical challenge to identify proper biochemical renal function measurements in patients with liver cirrhosis. Thus, until specific biomarkers become available, tailored choices of eGFR equations in the different clinical scenarios and stages of cirrhosis should be careful used.

Q1.3. What are the preferred urinary biomarkers of renal differential diagnosis in patients with liver cirrhosis?

The urinary biomarkers suggested in the differential diagnosis between ATN and pre-renal AKI, two forms of renal dysfunction associated with cirrhosis, are NGAL and IL-18 (1B).

Diagnostic accuracy and discrimination ability of Kim-1, L-FABP (liver-type fatty acid-binding protein) and Cystatin-C, require further data before a wide implementation in routine clinical practice could be recommended (2B).

Comment

Kidney damage parallels the dynamic and systemic nature of liver cirrhosis with possibly functional renal disease growing into structural damage. The role of urinary biomarkers in discriminating these entities are pivotal for addressing health care policies. Biomarkers able to predict reversibility of tubular damage are avenues requiring more studies.

Q2. Are there imaging techniques useful to diagnose the presence and extent of renal fibrosis in patients with chronic liver disease?

Direct assessments of renal fibrosis on biopsy samples are not routinely applied as percutaneous renal biopsy is difficult to perform due to abnormal coagulation and technical difficulties (Ungraded).

Diffusion-weighted MRI might be considered for the non-invasive assessment of renal fibrosis score (2B).

Comment

In this field, the presence and extent of renal fibrosis is a desired outcome. The promising findings reported in both preclinical and clinical studies using imaging techniques for the evaluation

of renal fibrosis require an expansion of studies identifying specific fibrosis score-induced changes to improve specificity and applicability.

Q3. Is there a typical histological pattern of kidney damage associated with liver disease?

IgA nephropathy is the most typical pattern of renal damage secondary to liver disease and especially related to alcoholic and viral cirrhosis (1A).

Comment

In circumstances where renal biopsy provides important information not only on the exact definition of the renal damage type but also to exclude other associated conditions, searching for a typical histological picture is mandatory whenever possible in patients with liver disease.

Q4. How and to what extent could contrast media be used in patients with associated liver and kidney failure?

Diabetes and ascites are the main risk factors for CIN in the presence of CKD (and especially in the presence of GFR < 30 mL/min) (1A).

Prophylactic measures such as renal replacement therapy, pharmaceutical agents and intravenous crystalloid have not been proved to improve the incidence of CIN (B).

A multidisciplinary discussion between radiologists and physicians must be encouraged and, in patients at risk for CIN, non-iodinated contrast studies (contrast-enhanced ultrasound or MRI), as well as the use of newer gadolinium-based contrast agents, may be useful (2C).

Comment

A clinically significant diagnostic advantage is suggested to be necessary for deciding if and how to expose a high-risk population to a radiological procedure with the potential of renal toxicity. Renal sparing contrast media are awaited.

Q5. To what extent does liver dysfunction have an impact on the assessment of renal function in the presence of liver cirrhosis complications (ascites, jaundice, malnutrition)?

In patients with CLD, kidney dysfunction measurements are underestimated in the presence of ascites, hyperbilirubinemia and malnutrition (1A).

Among different eGFR equations, the CKD-EPI equation that combines sCr and cystatin C measurements might be suggested for the accurate estimation of GFR in cirrhosis (1B).

MDRD-6 equations and use of the "Grail" formula might be useful for the estimation of renal function in the critical low range of <30 mL/min (1B).

Comment

Ascites, jaundice and malnutrition, among the capital clinical signs of liver dysfunction, had been demonstrated to significantly interfere with the assessment of renal function in cirrhosis. Among the different modified GFR equations and formulas, the issue is the choice of a proper formula at individual patient level in respect to critical GFR cut-off and medical need, whether diagnostic or therapeutic.

3. Acute kidney injury in liver cirrhosis

3.1. Diagnosis of AKI in liver cirrhosis

According to the Acute Kidney Injury Network criteria already used for the definition of AKI in the general population and to the KDIGO guidelines, the International Club of Ascites (ICA) defined AKI in cirrhosis by any of the following criteria: 1) increase in sCr by ≥0.3 mg/dL within 48 hours; or 2) a percentage increase in sCr ≥50% from baseline, which is known or presumed to have occurred within the prior 7 days [48,49].

Thus, diagnosis of AKI is now based also for cirrhotic patients on small changes in sCr with respect to previous values, rather than relying on a fixed cut-off value of sCr (>1.5 mg/dL).

Recently, a third criterion from the KDIGO guidelines (urine volume < 0.5 mL/kg/hour for ≥ 6 h) was suggested also for patients with cirrhosis [50], based on the evidence that evaluation of urine output in critically ill cirrhotic patients was shown to have a significant value in identifying patients with AKI and in predicting their prognosis, even in the absence of sCr elevations [51]. It should be noted that, to avoid misclassifications due to inaccurate urine collection, this criterion would only apply when obtained through a urinary catheter.

The current definition of AKI in cirrhosis is summarized in Table 1.

This definition entails the presence of a baseline sCr: a value of sCr obtained in the previous 3 months whenever available can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used.

In patients without a previous sCr value, the sCr at admission should be used as baseline [49].

Table 1
International Club of Ascites (ICA) new definitions for the diagnosis and staging of AKI in patients with cirrhosis.

Subject	Definition
Baseline sCr	A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used In patients without a previous sCr value, the sCr on admission should be used as baseline
Definition of AKI	Increase in sCr ≥ 0.3 mg/dL (≥26.5 µmol/L) within 48 h; or percentage increase sCr ≥ 50% from baseline which is known, or presumed, to have occurred within the prior 7 days; and/or urinary output ≤ 0.5 mL/Kg B.W. ≥ 6 h*
Staging of AKI	Stage 1: increase in sCr ≥ 0.3 mg/dL (26.5 µmol/L) or an increase in sCr ≥1.5-fold to twofold from baseline. AKI 1A (sCr at diagnosis < 1.5 mg/dl) and AKI 1B (sCr at diagnosis > 1.5 mg/dl) Stage 2: increase in sCr >two to threefold from baseline Stage 3: increase of sCr > threefold from baseline or sCr ≥ 4.0 mg/dL (353.6 µmol/L) with an acute increase ≥0.3 mg/dL (26.5 µmol/L) or initiation of renal replacement therapy

AKI, acute kidney injury; sCr, serum creatinine.
* for this evaluation a urinary catheter is needed. This parameter was recently suggested as part of the definition of AKI in cirrhosis [50] and requires validation in future studies.

Table 2
Diagnostic Criteria for HRS-AKI in cirrhosis.

Cirrhosis with ascites;
Increase in sCr≥ 0.3 mg/dL within 48 hrs or ≥ 50% from baseline value according to ICA consensus document [49] and/or urinary output ≤ 0.5 mL/Kg B.W. ≥ 6 h;
No full or partial response, according to the ICA consensus document [49] after at least two days of diuretic withdrawal and volume expansion with albumin at the recommended dose of albumin is 1 g/kg of body weight per day to a maximum of 100 g/day;
Absence of shock;
No current or recent treatment with nephrotoxic drugs;
Absence of parenchymal disease as indicated by proteinuria > 500 mg/day, microhematuria (>50 red blood cells per high power field), and/or abnormal renal ultrasonography.

Both in the general population and in cirrhosis AKI can occur as a consequence of pre-renal, intra-renal or intrinsic (ATN, acute interstitial or glomerular renal diseases) and post-renal (acute obstructive nephropathy) causes. Additionally, patients with cirrhosis may also suffer from a specific kind of renal dysfunction, HRS, which must be considered in the differential diagnosis [52].

HRS type-1 is a form of AKI: its definition has therefore to fulfill the new ICA-AKI criteria. This syndrome has accordingly been renamed HRS-AKI. To date, there are no markers or laboratory tests specific for HRS and its diagnosis remains one of exclusion. The diagnostic criteria of HRS-AKI are shown in Table 2. The only change made with respect to the classical diagnostic criteria of HRS was removal of the cut-off value of sCr >1.5 mg/dL. Therefore, the current definition of HRS-AKI includes patients who meet ICA-AKI criteria and fulfill all diagnostic criteria of HRS, irrespective of the sCr value at diagnosis.

3.2. Staging of AKI in liver cirrhosis

AKI can be stratified into 3 different stages according to the severity of the changes in sCr. Stage 1 is defined as an increase in sCr ≥ 0.3 mg/dL or an increase in SCr ≥ 1.5-fold to 2-fold from baseline; stage 2 is defined as an increase in sCr > 2-fold to 3-fold from baseline and stage 3 is defined as an increase of sCr > 3-fold from baseline or sCr ≥ 4.0 mg/dL with an acute increase ≥ 0.3 mg/dL or initiation of renal replacement therapy [49] (Table 1). AKI stage 1 can be divided into 2 subgroups: AKI 1A (sCr at diagnosis < 1.5 mg/dL) and AKI 1B (sCr at diagnosis ≥ 1.5 mg/dL) [53]. This further distinction is due to the fact that these subgroups are characterized by different prognosis, AKI 1A patients having a much better prognosis than AKI 1B ones, similar to patients without AKI [13,54].

3.3. Pathophysiology of AKI in liver cirrhosis

Patients with decompensated cirrhosis have an increased risk of developing AKI if compared to the general population and to those with compensated cirrhosis. While in healthy individuals renal autoregulation maintains the renal blood flow constant independently of fluctuations in the arterial pressure, patients with advanced cirrhosis are characterized by a shift to the right of the renal autoregulation curve. In other words, for the same values of renal perfusion pressure, renal blood flow is lower than that of patients with compensated cirrhosis and in healthy subjects. This condition is probably the consequence of increased activity of the sympathetic nervous system in the context of the circulatory dysfunction typical of patients with advanced cirrhosis [55,56].

With this background, among the factors potentially leading to AKI, of particular importance are: the presence of infections, factors leading to hypovolemia, such as massive fluid losses (e.g., diarrhea or gastrointestinal bleeding), the use of paracentesis not followed by volume replacement with albumin infusions, the use of potentially nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors). Several recent studies have assessed frequency and types of AKI using the current definition among patients admitted to the hospital for decompensated cirrhosis. They found that the most common causes are hypovolemia-induced AKI (up to 50%), HRS-AKI (up to 43%) and ATN (up to 35%).

These and other factors act on a pathophysiological background where hemodynamic disturbances and systemic inflammation play a primary role in the development of AKI and particularly of HRS-AKI.

3.3.1. Systemic circulatory and cardiac dysfunction

Portal hypertension (PH) is the key pathophysiological mechanism responsible for the development of AKI in patients with end-stage liver disease (ESLD). PH leads, through the release of several vasoactive mediators (nitric oxide, prostacyclins, endocannabinoids and carbon monoxide among the many identified), to splanchnic and systemic vasodilatation with reduced effective arterial blood volume [57]. The reduction in mean arterial pressure (MAP) induces a systemic compensatory homeostatic response, in an attempt to counterbalance the hypotensive state, by activation of the renin-angiotensin-aldosterone system and sympathetic nervous system and an increase in cardiac output [58]. In the early stages of PH arterial pressure is therefore maintained at near normal values through these hemodynamic changes, but the following stages of the disease, when patients have already developed clinical decompensations, are characterized by further reduction in splanchnic and systemic vascular resistances together with a significant decrease of myocardial output caused by systolic and diastolic dysfunction, a syndrome defined as cirrhotic cardiomyopathy, which contributes to the hemodynamic disturbances. In an attempt to maintain the arterial pressure within values compatible with life, there is a further increase in the activation of endogenous vasoconstrictor systems and the non-osmotic hypersecretion of vasopressin from the pituitary gland. The vasoconstrictors keep the patients alive by maintaining the effective arterial blood volume within normal limits, but also have important detrimental effects on kidney function, with sodium and solute-free water retention, causing the accumulation of ascites and edemas. If the activation of these systems is extreme, they may lead to a marked vasoconstriction of the afferent vessels of the kidneys, with a subsequent reduction in renal perfusion and development of HRS [56,58,59].

3.3.2. Systemic inflammation

In this scenario, systemic inflammation and oxidative stress induced either by pathogen associated molecular patterns (PAMPs) (e.g., lipopolysaccharide and bacterial DNA) or by damage-associated molecular patterns (DAMPs) (e.g., high-mobility group protein B1 and heat shock proteins) play a crucial role in the development of organ failures, including the kidneys [9,60]. In the last years, it has been clearly described that decompensated cirrhosis is associated with marked and persistent systemic inflammation, which, regardless of the presence of overt bacterial infections, increases with the disease progression and is involved in the development of complications, such as AKI, which in fact is very common among patients with ACLF, a syndrome characterized by high levels of inflammatory markers [61]. Bacterial translocation (BT) from the gut to mesenteric lymph nodes is thought to be the main factor linking PH to inflammation in the mechanisms leading to AKI in cirrhosis. In fact, because of increased gut permeability related to portal hypertension, bacterial translocation develops and triggers an inflammatory response with release of pro-inflammatory cytokines, which lead to further splanchnic arterial vasodilation and circulatory dysfunction. In

detail, PAMPs deriving from BT (or from bacterial infections) and DAMPs released from the injured liver stimulate the circulating innate immune cells to produce and release proinflammatory cytokines, which then cause impairment of the renal function. The underlying mechanisms are not fully understood, but inflammatory mediators probably cause further renal vasoconstriction (acting on vascular smooth muscle cells) and direct kidney tissue damage (mainly of the proximal tubular epithelial cells) [62]. Among these cytokines, tumor necrosis factor alpha (TNF-α), IL-6, and IL-1β seem to play a pivotal role [63].

3.4. Pathology of AKI

In the last years several pieces of evidence suggest that HRS (now HRS-AKI) should no longer be recognized as a purely functional entity. It is now believed that this syndrome may have an additional structural component of some degree of renal parenchymal injury. This would at least in part explain the lack of response to pharmacological treatment with vasoconstrictors plus albumin observed in about 50% of patients. Patients with ESLD often have chronic kidney lesions due to comorbidities [e.g., hypertension and diabetes in patients with Non-Alcoholic Steato-Hepatitis (NASH)] and to presence of well-known specific causes of renal disease (e.g., IgA nephropathy in alcoholics, viral-induced glomerulopathy in HBV- and HCV-related cirrhosis). Moreover, many patients with HRS-AKI have jaundice and cholestasis and bile salt-related nephropathy per se may also contribute to renal dysfunction.

The presence of underlying renal lesions has been shown in renal biopsies also in cirrhotic patients without significant proteinuria/hematuria and ultrasonographic findings of CKD. In other words, the correlation between conventional markers of CKD (i.e. clinical presentation) and renal histology findings has been shown to be quite poor [26].

In this context, urinary biomarkers of tubular injury have been extensively investigated, particularly NGAL. If, on one hand, it has been proven that its levels are higher in the presence of ATN compared to patients with HRS or pre-renal AKI [17], on the other it has been shown that the levels of several urinary biomarkers of tubular injury are increased (even if often to a lower extent compared to ATN) also in patients with HRS-AKI, suggesting a continuum between functional and structural renal dysfunction in patients with cirrhosis and providing a new concept of AKI with possible therapeutic and prognostic implications for these patients [64]. However, it should be noted that none of these investigations on urinary biomarkers of tubular injury included renal histology as gold standard. Thus, the differential diagnosis between “pure” functional HRS-AKI, HRS-AKI with minor intrinsic renal damage and ATN remains difficult.

3.5. Clinical impact of AKI on compensated/decompensated liver cirrhosis

AKI is a common complication in patients with cirrhosis, occurring in up to above 50% in patients admitted to hospital for liver disease complications [54,65].

The development of AKI is associated with high morbidity and mortality in cirrhosis, correlating with both initial and peak AKI stage (the higher the stage, the worst the prognosis) and with the existence of treatments potentially able to reverse it [53,54]. Furthermore, cirrhotic patients with severe or repeated episodes of AKI are at higher risk of developing CKD than the general population. The prognosis markedly differs according to the cause of AKI. In a study performed before the ICA-AKI era, it was clearly demonstrated that the three-month transplant-free survival probability was far lower for patients with HRS than for patients with parenchymal nephropathy or hypovolemia-induced renal failure, confirming that among the possible different types of AKI, HRS has certainly the worst prognosis [66,67].

3.6. Prevention of AKI

Considering the worse outcome of patients developing AKI in comparison with patients without renal dysfunction, AKI prevention and/or early identification are of paramount importance in patients with ESLD. For this purpose, when dealing with patients with cirrhosis, especially if decompensated, clinicians should always:

- avoid potentially nephrotoxic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), vasodilators and, if possible, certain antimicrobial medications, particularly aminoglycosides and amphotericin;
- avoid unnecessary high doses of diuretics (use diuretics at their minimum effective dose);
- improve the hemodynamics by plasma volume expansion in patients with clinically proven or even suspected hypovolemia (crystalloids in the case of diarrhea or excessive diuresis; red packed cells in the case of severe bleeding). In patients submitted to large-volume paracentesis, concentrated (20–25%) albumin infusion 8 gr/L of ascites removed is used, as it decreases the incidence of paracentesis-induced circulatory dysfunction (PICD), thus preventing the development of AKI and improving patient survival [68];
- recognize and treat bacterial infections promptly. Particular attention should be paid to spontaneous bacterial peritonitis, whose timely treatment with albumin infusion (1.5 g/kg at diagnosis followed by 1 g/kg on day three) in addition to antibiotics has been shown to decrease the development of renal failure, thereby improving the survival rate [69];
- administer empiric antibiotic therapy for the prevention of bacterial infections in patients with portal-hypertension related bleeding, as infections may result in the development of HRS-AKI [70,71];
- prevent the onset of spontaneous bacterial peritonitis (SBP) in patients at high risk (Child-Pugh score $\geq$ 9 and serum bilirubin level $\geq$3 mg/dL, with either impaired renal function or hyponatremia, and ascitic fluid protein lower than 15 g/L) (primary prophylaxis) [72];
- prevent a new onset of SBP in patients who recovered from a first episode (secondary prophylaxis) [72];
- avoid and/or use alternatives to radiocontrast procedures, if not absolutely needed, even though it is uncertain if contrast media represent a real cause of AKI in cirrhosis [73].

3.7. Treatment of AKI

Once AKI in general, and HRS-AKI in particular, is diagnosed, it should be managed as soon as possible, in order to prevent its progression to more advanced stages, in accordance with what was recently proposed in the new European guidelines for the management of patients with decompensated cirrhosis [68]. All possible precipitating factors should be identified and properly treated (discontinued in the case of nephrotoxic drugs, treated in the case of hypovolemia or infections) [49]. According to the new definition of HRS-AKI, complete response to the treatment is defined by a final sCr within 0.3 mg/dL (26.5 µmol/L) from the baseline value; partial response is defined by the regression of AKI stage to a final sCr $\geq$ 0.3 mg/dL (26.5 µmol/L) from the baseline value [68]. Most pre-renal AKI cases can be easily diagnosed on the basis of patients’ recent medical history together with their clinical picture and resolved by plasma volume expansion. Crystalloids are the treatment of choice in the case of AKI induced by

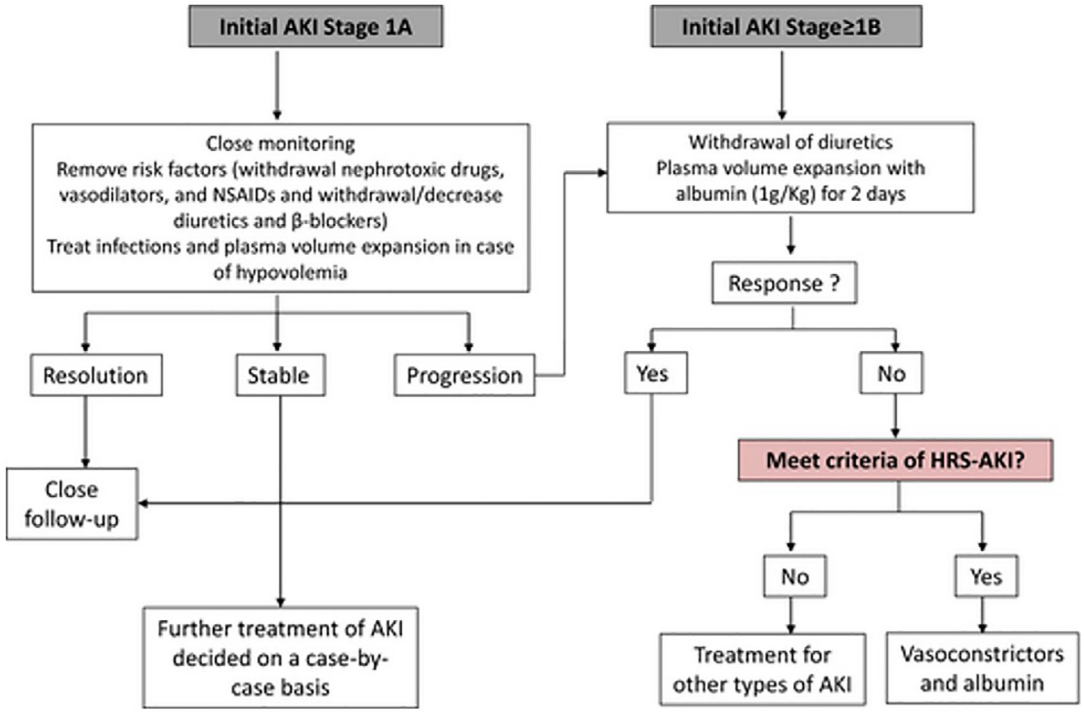

Fig. 1. Algorithm for the diagnosis and management of AKI in patients with cirrhosis.

diarrhea or excessive diuresis; packed red blood cells in the case of bleeding, in order to maintain serum hemoglobin levels between 7 and 9 mg/dL [74]. Moreover, volume expansion is important for both the treatment and differential diagnosis of AKI. In the case of AKI stage > 1A of undetermined cause or with no response to the initial treatment, albumin should be given for two consecutive days (1 g of albumin/kg of body weight, with a maximum of 100 g/day) in order to exclude central volume depletion as cause of AKI [68,75]. Post-renal AKI is rare and should be treated in accordance with the cause of the obstruction [52]. Consequently, the real clinical challenge is the treatment of HRS-AKI. Fig. 1 shows the algorithm for the diagnosis and management of AKI in cirrhosis.

3.7.1. HRS-AKI

Pharmacological treatment

Treatment of HRS-AKI is based on vasopressors (terlipressin, a vasopressin analogue that is the most investigated vasoconstrictor in HRS, and alpha-adrenergic agonists, such as noradrenaline and midodrine) plus albumin infusions. Vasoconstrictors act by directly counteracting the splanchnic arterial vasodilation characteristic of these patients, while albumin is thought to act by both its oncotic and non-oncotic (mainly antioxidative and anti- inflammatory) properties, improving the effective circulating volume, vascular resistances and cardiac contractility [76]. Albumin should be given in association with vasopressors at a dose of 1 g/kg body weight the first day followed by 20–40 g/day.

Terlipressin

Several randomized studies have shown that terlipressin improves renal function in a significant proportion of patients with HRS-1 (about 50% of patients) and that patients responding to treatment show a better survival than non-responders [77,78].

Moreover, this last result was confirmed by three meta-analysis of randomized trials, where the use of terlipressin was associated with a significant improvement in short-term survival, a result that must be considered in candidates for LT [79,80].

The 3-month transplant-free survival being very low (below 50%) even in responders [81] vasoconstrictors must be considered only as a bridge to transplantation. In other words, LT represents the optimal and only resolutive treatment for patients with HRS-AKI regardless of their response to pharmacological treatment. In this setting, responders may be disadvantaged by the improvement in sCr induced by terlipressin, as their MELD score is temporarily reduced, and this can delay the timing of LT. Therefore, in responders to therapy it has been suggested to use the baseline MELD score before treatment or to consider the pharmacological treatment of HRS as dialysis in the calculation of the MELD score [82].

The traditional dose of terlipressin is 1 mg every 4–6 hours as intravenous boluses; in the case of reduction in sCr of less than 25% from baseline after 3 days of treatment, the dose should be increased to 2 mg every 4–6 hours. Treatment should be maintained until complete response or for a maximum of 14 days [83]. The most common adverse events observed during therapy with terlipressin are diarrhea and abdominal cramps, which are usually mild and transient. However, severe and potentially dangerous adverse effects have also been described, such as angina, cardiac arrhythmias (mainly bradycardia), severe hypertension and intestinal, finger, tongue, scrotum and skin ischemia [83].The frequency of adverse events leading to treatment withdrawal is quite high, approximately 20% of all treated patients, thus representing a relevant issue. In the case of adverse events, terlipressin should be discontinued or tapered, according to the severity of the symptoms, and patients should be closely monitored.

Administration of terlipressin by continuous intravenous infusion (starting with 2 mg/day) has been shown, when compared to the traditional boluses administration, to have similar percentages of response to treatment (76% vs. 65%, respectively; p=ns) and to be better tolerated, with a significant reduction of adverse events (35% vs. 62%, respectively; $p < 0.025$), probably related to the fact that the mean daily effective doses of terlipressin were significantly lower in the continuous infusion group [84].

Two important predictive factors of response to treatment with terlipressin and albumin should be mentioned. Beside baseline sCr levels (that were previously mentioned and will be further discussed later), it has been observed that the presence of ACLF and its severity (i.e. number of organ failures) significantly affects the prognosis. In other words, the more severe ACLF is (and consequently the more severe is the systemic inflammatory state), the lower the probability of response to treatment [85].

Noradrenalin

Noradrenaline plus albumin appears to be as effective as terlipressin plus albumin for the management of type-1 HRS and these results were confirmed in a recent meta-analysis [86]. Thus, noradrenalin seems to be a valid alternative to terlipressin in these patients, and this is especially important for those countries where terlipressin is not available. However, three points deserve to be outlined. First, the overall number of type-1 HRS patients treated with noradrenaline is still too small to suggest it as first line treatment for these patients; second, the evidence gathered so far is based on low-quality trials; third, in patients with ACLF (defined by Asian Pacific Association for the Study of the Liver criteria) noradrenalin was suggested to be significantly less effective than terlipressin in the treatment of HRS-AKI (reversal of HRS in 17% vs. 40%; $p = 0.004$ respectively), probably because, unlike terlipressin, noradrenalin does not reduce the portal pressure [87].

Therefore, taking all these aspects into account, further high quality studies are needed to clarify the role of noradrenalin in the treatment of HRS-AKI.

Midodrine and octreotide

The effectiveness of treatment with midodrine (an alpha1-agonist) in combination with octreotide (a somatostatine analogue) and albumin was proven in patients with HRS-AKI in terms of both renal function and transplant-free survival (when compared with treatment with dopamine) [88].

However, when compared with terlipressin, treatment with midodrine plus octreotide was far less effective at achieving a complete response in HRS-AKI patients (70% vs. 29%, $p = 0.01$).

Non-pharmacological treatment

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

A TIPS is a stent placed via a transjugular approach within the liver that connects the portal vein with one of the hepatic veins. It is a pathophysiological treatment of portal hypertension, as it lowers portal pressure and, doing so, relieves circulatory dysfunction and improves renal function in cirrhotic patients with ascites [89]. However, this procedure has limited use as a treatment for HRS-AKI, because of the poor liver function characteristic of these patients. In fact, the relative liver ischemia that follows TIPS insertion can aggravate the already limited liver reserve of these patients and precipitate liver failure. TIPS is therefore a therapeutic option only for a very limited group of selected patients with HRS-AKI, with relatively preserved liver function.

Renal Replacement Therapy

Renal replacement therapy (RRT) has no role in the management of HRS-AKI in cirrhosis as first- line treatment, as it does not provide any significant advantage in terms of increased survival [90] RRT can be used as rescue therapy in patients non-responders to vasoconstrictors plus albumin, who are on the liver transplant waiting list or as “extrema ratio” even in those non-candidates for liver transplant, for a limited duration trial.

The decision to initiate continuous RRT should be based on both clinical grounds and laboratory values. The clinical indications for RRT are, as for the general population, severe metabolic acidosis and/or electrolyte disturbances (mainly hyperkalemia or hyponatremia) non-responding to pharmacological management and oliguria with volume overload in patients with diuretic resistance or intolerance. An individualized patient-specific approach should be used

Alternative dialysis methods

Alternative dialytic methods for the management of type-1 HRS such as the Molecular Adsorbent Recirculating System (MARS) [91] or fractionated plasma separation and adsorption (Prometheus) [92], have been proposed. These methods are based on removal from the systemic circulation of several substances that are believed to play an important role in the pathogenesis of HRS, including endogenous vasodilators, bacterial products and inflammatory cytokines. Despite in principle those techniques may have some potential beneficial effects, we believe that MARS has not a real role in the treatment of renal dysfunction in decompensated cirrhosis, acute on chronic liver failure and HRS-AKI. Thus, further studies are needed to define their role in HRS-AKI.

Liver transplantation

Patients with HRS-AKI have a very poor prognosis, irrespective of their response to medical treatment. In this context, LT represents the only definitive treatment for patients with HRS-AKI and is therefore the treatment of choice.

3.8. The relationship between AKI and CKD

Acute renal failure in cirrhosis may be classified as:
Functional

- responding or not responding of plasma volume expansion (pre-renal, and HRS) theoretically reversible

Structural

- such as ATN also reversible in 3–6 weeks but independently of LT

Recent studies have suggested that AKI and CKD are not two clinical and physiopathological entities; moreover, the term AKI emphasized a vision that includes all the causes of kidney damage and considered a continuous progression from functional to structural damage and eventually to chronic kidney disease.

Many observational studies actually reported that a substantial proportion of patients with AKI could recover renal function but then have progression to advanced stages of CKD [93–95].

However, AKI is a risk factor for transition to CKD secondary to nephron loss and hyperfiltration, ischemia, and maladaptive repair mechanisms, which cause incomplete recovery and evolution to CKD [96].

In this new vision the natural history of AKI first begins by a decrease of GFR usually followed by ischemia and in the last phases with structural tubular lesions.

Even in cirrhotic patients we have strong arguments to consider AKI in cirrhosis as a continuous disease from functional (pre-renal and HRS) to structural (ATN) with an overlap between different phenotypes; in hepatorenal syndrome, in which LT theoretically reverses hemodynamic changes and fully reverses HRS, we observe that some patients do not fully recover, suggesting unrecognized irreversible kidney damage leading to acute tubular damage.

Moreover staging of AKI has been associated to different phenotype of renal injury; a recent prospective study with over 500 patients revealed that pre-renal was more frequent in stage 1a, ATN was frequent in stage 3, while HRS was equally distributed between stage 1b and stage 3 [54]. This study seems to confirm the concept of transition from functional (mostly reversible and less severe) to structural (frequently irreversible and more severe) AKI.

In the general population there are several mechanisms of tissue repair in AKI such as tubular proliferation, resolution of inflammatory infiltrates, endothelial repair and regeneration which leads to restore normal kidney function in 90% of cases. Factors leading to maladaptive repairs and/or disordered regeneration involved in progression from AKI to CKD are aging, previous AKI, oxidative stress, prolonged hypoxia; all these are frequently present in cirrhosis [97]. Moreover many cirrhotic patient with AKI, in particular those with a comorbidity such as hypertension and diabetes, have underlying CKD and the presence of well-known specific causes of renal disease (e.g., Ig A nephropathy in alcoholics, viral-induced glomerulopathy in HBV- and HCV-related cirrhosis). The presence of underlying renal lesions has been shown in renal biopsies also in cirrhotic patients without significant proteinuria/hematuria and ultrasonographyc findings of CKD. In other words, the correlation between conventional markers of CKD and biopsy finding has been shown to be poor [26].

How can we differentiate between reversible and not reversible AKI and identify patients at a higher risk of progressing from CKD? How can we recognize patients more susceptible to developing irreversible ATN leading to CKD and those with previous underlying chronic kidney disease? Given that 10% of ATN develop irreversible kidney disease, we should develop biomarkers predicting reversibility or irreversibility of kidney failure.

The effort to identify pre-transplant clinical and biochemical criteria that may identify acute and reversible from chronic kidney injury could be of huge importance in order to avoid combined liver-kidney transplant in recipients with reversible kidney injury and, on the other hand to identify patients in whom KT should be considered.

In clinical practice AKI staging as a good prognostic value, and the absence of terlipressin response should be useful to differentiate HRS which is reversible from ATN which may be also reversible but independently of terlipressin or LT, moreover the ability to predict potential recovery is mainly related to clinical issues such as duration of low eGFR or renal replacement therapy.

The prospective study by Maiwall et al. evaluating more than 800 consecutive patients with cirrhosis revealed that almost two-thirds of patients with cirrhosis develop episodes of AKI and reduction in GFR; a third progress to CKD, resulting in adverse outcomes. Higher MELD, CystC levels, prior AKI episodes were identified as significant and independent risk factors for CKD [31]; this could be explained by the fact that at every AKI episode there is a loss of functional nephrons with a consequent loss of functional reserve.

Changes in sCr, eGFR are not useful in predicting reversibility or the progression toward irreversibility and CKD, other current biomarkers such as uNa, hematuria, proteinuria have poor accuracy.

Emerging biomarkers such as NGAL KIM-1 which are all tubular biomarkers induced by ischemia whatever the cause of AKI, markedly increased in ATN, but there are many overlaps between phenotype and no clear cut-off has been defined [16,18,64]. New biomarkers involved in matrix remodeling and fibrogenesis seem to be the best candidates for predicting reversibility or irreversibility.

In this field, osteopontin, a glycoprotein induced by an inflammatory process in AKI [98] and TIMP-1 appears to play an important role in recovery of sepsis-related AKI [99].

A recently published reverse trial evaluated a cohort of patients undergoing LT alone in order to validate a pre-LT model predictive of renal function recovery after LT [100].

The study analyzed three groups of patients pre- and 4 and 12 weeks post-OLT divided according to reversibility of kidney failure and showed that post-transplant renal recovery in patients with pre-LT AKI was related with a higher decline of OPN and TIMP-1 levels at 4 weeks.

3.9. The relevance and management of AKI in liver transplant setting

The occurrence of renal dysfunction before or after LT represents a complicated, multifaceted and critical issue that adversely affects the outcomes.

AKI occurs commonly in patients with liver cirrhosis, with rates of about 19–49% [13,53,56,101–105], and negatively influences patient survival prior to and after LT [13,53,101,103]. AKI in patients with cirrhosis commonly occurs due to large volume loss, HRS due to vasoconstriction and reduced renal blood flow and ATN, due to prolonged pre-renal factors, sepsis, or nephrotoxic agents [105–108].

In advanced liver cirrhosis, AKI can be triggered spontaneously or as a result of infections, gastrointestinal bleeding, large volume paracentesis, or surgery [65,96,109], and so all of these factors should be treated as early as possible to avoid its occurrence.

In the pre-LT setting, an assessment of reversibility of renal injury is mandatory. It is important to understand both the etiology and chronicity of renal dysfunction because the treatment clearly varies, especially with respect to choice of combined or simultaneous liver-kidney transplantation.

Despite widespread use, changes in sCr or eGFR are not sensitive enough to predict the degree or course of renal injury, particularly in patients with cirrhosis and malnutrition [44,110–113]. Thus, big efforts are currently made to incorporate biomarkers that may enhance clinical prediction of renal recovery after LT [114,115].

During the intra-operative period, there are often major hemodynamic changes and bleeding, which occasionally cause low blood pressure that may lead to severe renal hypoperfusion.

During the immediate postoperative period, many other conditions are related to the development of renal dysfunction, including the presence of severe cardiovascular disease, cardiomyopathy, prolonged episodes of hemodynamic instability, low blood pressure, severe depletion of intravascular volume, the use of drugs that adversely affect intrarenal hemodynamics, advanced age, and previous stable kidney diseases.

Pre-existing renal dysfunction is associated with many adverse outcomes after LT, including inferior short- and long-term patient survival [116–118], increased costs [118], post-transplant sepsis, longer intensive care unit stays and the need for dialysis [119]. It has been recently shown that in patients with AKI-HRS listed for LT, response to terlipressin and albumin significantly reduced the need for RRT and the risk of CKD at 1 year after LT [120].

The predisposing factors for renal dysfunction in transplant recipients include drugs toxicity and other disorders related to the severity of the patient's condition and allograft dysfunction [121,122]. Nephrotoxic drugs include iodinated contrasts, antibiotics (mainly aminoglycosides, amphotericin Band aciclovir), treatment with immunosuppressive drugs such as calcineurin

inhibitors (CNI, cyclosporine and tacrolimus), prolonged dopamine or vasopressor administration and multiple transfusions.

Several pharmacological strategies are frequently adopted in the earlier post-LT phase to improve renal function: osmotic diuretics that are recommended in cases of volume overload, low doses and/or delayed introduction of CNI, in combination with anti- IL-2 receptor antibodies and/or mycophenolate (MMF), continuous hemodiafiltration or conventional hemodialysis.

Questions

Q6. What is the definition of AKI in liver cirrhosis?

In patients with cirrhosis the diagnosis of AKI relies on ICA-adapted KDIGO criteria and is based on small changes in sCr (either an increase of ≥ 0.3 mg/dL from baseline within 48 h, or an increase of ≥ 50% from baseline within three months) (1A).

Recently, it has been suggested that urinary output (urine volume <0.5 mL/kg/hour for ≥6 h) can provide a significant advantage in identifying patients with AKI and in predicting the prognosis of critically-ill cirrhotic patients (2B).

All types of AKI can occur in patients with cirrhosis, as in the general population: pre-renal, intrinsic and post-renal. Additionally, patients with cirrhosis can develop a specific kind of AKI, the HRS-AKI (1A).

A diagnosis of HRS-AKI is by exclusion and is based on the revised ICA criteria (1B).

Comment

AKI in cirrhosis has been redefined adapting the KDIGO criteria in the setting of cirrhosis and relies now on changes in sCr, without any fixed threshold value (1.5 mg/dL). The key feature of the revised definition of AKI in cirrhosis is that it is dynamic and that even minor increases in sCr are sufficient to meet the definition and make a prompt diagnosis of AKI, for potential early interventions.

Accordingly, any cut-off value has also been removed from the definition of HRS-AKI. Traditionally, type-1 HRS was characterized by rapidly progressive renal failure (a sCr value doubled from baseline to a final value >2.5 mg/dL in less than 2 weeks) with very low survival (median of less than 1 month if untreated). It has been clearly shown that the higher the sCr value at the beginning of treatment with vasoconstrictors and albumin, the lower the probability of response, with poor survival. These data suggest that the traditional approach of waiting for a predetermined value of sCr to start treatment may decrease the probability of response compared to an approach based on an earlier treatment. The most relevant advantage of the current definition of HRS-AKI is therefore that it will lead to an earlier identification and treatment of this syndrome, hopefully improving its efficacy.

Q7. What is the staging of AKI in liver cirrhosis?

The staging of AKI should be based on an ICA-adapted KDIGO staging system, thus distinguishing between (1A):

- AKI stage 1: increase in sCr ≥ 0.3 mg/dL (26.5 μmol/L) or an increase in sCr ≥ 1.5-fold to 2-fold from baseline; AKI stage 1 is differentiated into 1A and 1B, according to the value of sCr at diagnosis, <1.5 or ≥1.5 mg/dL, respectively;
- AKI stage 2: increase in sCr > 2-fold to 3-fold from baseline;
- AKI stage 3: increase in sCr > 3-fold from baseline or sCr ≥ 4.0 mg/dL (353.6 μmol/L) with an acute increase ≥0.3 mg/dL (26.5 μmol/L) or initiation of renal replacement therapy

Comment

A staging system of AKI based on changes in sCr enables an accurate assessment not only of the presence of AKI, but also of the severity of renal dysfunction. This is crucial, as different stages of AKI correspond to different prognoses (the higher the grade, the worse the prognosis) and the progression of AKI through stages correlates with an increased mortality [13,53,123].

Q8. What is the pathophysiology of AKI in liver cirrhosis?

AKI pathophysiology in cirrhosis, and particularly that of HRS-AKI, is characterized by systemic hemodynamic disturbances and inflammation, both of which increase in parallel with the progression of the liver disease (1A).

HRS-AKI, besides being a functional syndrome, can also have an additional structural component of some degree of renal parenchymal injury (2C).

Among the different biomarkers of tubular injury, urinary NGAL may be used to help in distinguishing between ATN and HRS-AKI (2B).

Comment

The well-established hemodynamic disturbances characteristic of decompensated cirrhosis and a systemic inflammatory state not yet known in its entirety but well- described in recent years are of paramount importance in the development of AKI and particularly of HRS-AKI. However, if on one hand this is undoubtedly true, on the other it is increasingly evident that HRS-AKI may not be a purely functional syndrome, with (at least in a proportion of cases) an additional component of renal parenchymal injury. In this context, NGAL has been shown to be a promising test to distinguish between structural AKI (patients with ATN having the highest NGAL levels) and functional AKI (those with pre-renal azotemia showing the lowest NGAL values), with intermediate values in patients with HRS-AKI. To recognize which part of AKI is prevalent (structural or functional) is certainly among the most important future challenges for researchers dealing with decompensated cirrhosis, due to its possible therapeutic and prognostic implications in clinical practice.

Q9. What is the clinical impact of AKI on compensated/decompensated liver cirrhosis?

AKI is very common among cirrhotic patients admitted to hospital for decompensated liver disease (1A).

The development of AKI is associated with high morbidity and mortality in cirrhosis, correlating with AKI stage (1A).

Comment

AKI is a well-known and common complication in patients with advanced cirrhosis. Many studies have proven AKI as an independent predictor of mortality, depending on the severity of renal dysfunction (i.e. AKI stage) and type of AKI, patients with HRS-AKI and those with ATN having the worst prognosis.

Q10. What are the prevention strategies for AKI in compensated/decompensated liver cirrhosis?

Potentially nephrotoxic agents (such as NSAIDs, vasodilators, aminoglycosides, amphotericin, high doses of diuretics) should be avoided or, if essential for the patient, used with extreme caution (1A).

In the case of hypovolemia, fluids replacement (crystalloids or red packed cells) should be started immediately according to the kind and severity of the fluid losses (1A).

In patients with tense ascites, large-volume paracentesis (> 5 L) should be followed by concentrated (20–25%) albumin infusion 8 g/L of ascites removed to prevent PICD-related AKI (1A).

Screening and treatment of infections must be a priority in cirrhotic patients (1A).

In cirrhotic patients with acute gastrointestinal bleeding antibiotic prophylaxis is recommended because it reduces the incidence of infections (1A).

Patients with SBP should receive albumin (1.5 g/kg at diagnosis followed by 1 g/kg on day three) to prevent AKI (1A).

Patients should be given norfloxacin (400 mg/day) for primary or secondary prevention of SBP, in order to prevent SBP-induced AKI (1A).

Comment

Patients with cirrhosis share with the general population many possible precipitating factors of AKI that, as in the latter patients, should be avoided (e.g. volume depletion and nephrotoxic drugs). However, clinicians dealing with patients with cirrhosis must also tackle disease-specific triggers of AKI (e.g. PICD and SBP) for which a prophylactic strategy must be put into practice with the aim of reducing the risk of AKI as much as possible.

Q11. What are the treatment strategies for AKI in compensated/decompensated liver cirrhosis?

Any drug potentially associated with renal dysfunction (such as NSAIDs, vasodilators, aminoglycosides, amphotericin, diuretics, beta-blockers) should be stopped immediately or, if not possible, reduced (1A).

In the case of overt hypovolemia, fluids replacement should be started immediately based on the cause and severity of the losses (1A).

In the case of AKI stage >1A of undetermined cause or of AKI with no response to the initial treatment, albumin should be given at a dose of 1 g of albumin/kg of body weight (with a maximum of 100 g of albumin) for two consecutive days (1C).

In the case of HRS-AKI, terlipressin plus albumin infusions is the first-choice treatment and should be started as soon as possible (1A).

Concentrated (20%) albumin solutions should be given at a dose of 1 g/kg body weight the first day followed by 20–40 g/day, monitoring central blood volume in order to avoid circulatory overload (1B)

Noradrenaline can be an alternative to terlipressin, but so far information is limited and high quality studies are needed to clarify its efficacy (2A).

Midodrine plus octreotide is not a valid alternative (unless neither terlipressin nor noradrenalin are not available), as this treatment is much less effective than terlipressin (1A).

The applicability of TIPS is very limited in this setting; available data do not allow it to be advocated in HRS-AKI (2B).

RRT is not a first-line treatment for HRS-AKI and should be considered only as rescue therapy in patients non-responders to vasoconstrictors plus albumin, based on standard criteria for RRT (2B)

Data from alternative dialytic methods are very limited and results unsatisfactory. Therefore, so far they cannot be advocated for HRS-AKI (2C).

LT is the best and only definitive treatment for patients with HRS-AKI, irrespective of the response to pharmacological therapy (1A).

Comment

When AKI is diagnosed, a specific treatment (if available, depending on the type of AKI) should be started as soon as possible and general supportive measures should be undertaken in order to reduce as much as possible the risk of AKI progression to more severe stages and to restore the baseline kidney function. Fluid balance and vital signs should be carefully monitored. All possible precipitating factors should be investigated and properly removed or treated, with particular attention to the presence of bacterial infections.

In case of HRS-AKI, treatment is based on vasopressors plus albumin infusions. Several randomized studies and meta-analysis during the last two decades have shown that terlipressin should be the treatment of choice.

It must be highlighted that almost all the results obtained so far in the treatment of these patients were derived from studies including patients with HRS-1 according to the old ICA definition, where a sCr > 2.5 mg/dL was needed for the diagnosis of HRS-1. In this context, higher baseline sCr values were shown to be a strong independent predictive factor of no response to therapy. To date, data reporting the efficacy of vasoconstrictors and albumin in patients with HRS-AKI are very scant, especially in patients with sCr lower than 2.5 mg/dL. Whether the new definition of HRS (HRS-AKI), which will surely imply an earlier start of treatment, lead to increased rates of response to therapy will have to be assessed in the near future.

Q12. What is the relationship between AKI and CKD?

AKI is a risk factor for transition to CKD secondary to nephron loss and hyperfiltration, ischemia, and maladaptive repair mechanisms, which cause incomplete recovery and evolution to CKD (2C).

Even in cirrhosis, a transition from functional AKI (mostly reversible and less severe) to structural (frequently irreversible and more severe) AKI and lastly to CDK was confirmed (2C).

In cirrhosis, factors leading to maladaptive repairs such as aging, previous AKI, oxidative stress, prolonged hypoxia are frequently present (2B).

New biomarkers such as osteopontin and TMP-1 appear to be the better candidates for predicting AKI reversibility or irreversibility (2C).

Comment

Even in cirrhosis, as in the general population, AKI and CKD are not two separate clinical identities but a continuous progression from functional and potentially reversible injury to structural and irreversible damage, which could lead first to ATN and subsequently to CKD.

The tissue repair mechanism could be particularly compromised in cirrhotic patients in whom the chronic inflammatory state, as well as oxidative stress, and infections can promote the progression from acute reversible to chronic irreversible kidney injury

Q13. What is the relevance and management of AKI in waiting-list patients?

Renal dysfunction is a critical determinant of outcomes in patients with ESLD and the early identification and assessment of functional (transient injury from alterations in perfusion) and structural causes (irreversible damage to the renal parenchyma) are mandatory in patients undergoing LT (2A).

Pre-transplant AKI is a predisposing factor for both post-operative AKI and CKD and both are associated with increased morbidity and mortality (1A).

Prevention of AKI prior to LT includes the avoidance and timely correction of hypovolemia, the avoidance of potentially nephrotoxic drugs, the prevention and prompt recognition and treatment of infections (2A).

Several kidney biomarkers have been evaluated to allow earlier diagnosis of AKI cause (i.e., hepato-renal syndrome vs. ATN), and differentiate reversible from permanent renal changes (2B).

AKI should be considered in all cirrhotic patients with increased sCr and oliguria, or worsening oliguria/anuria alone, as decreased urine output is a sensitive and early indicator of AKI and is associated with poorer outcomes (1A).

The management of AKI prior to LT includes volume expansion and is based on vasopressors (mainly terlipressin) plus albumin infusions in the cases of HRS (1A).

A complete response to terlipressin therapy is achieved in about 50% of patients and the 3-month transplant-free survival is low (<50%) even in responders (2A); thus, terlipressin should be considered a valid approach as a bridge to LT (2B).

In patients awaiting LT, the response to terlipressin therapy and the improvement in sCr can cause an unsuitable reduction in MELD score, delaying the timing of LT (A); it has thus been suggested to use the baseline MELD score (before treatment) or to consider the pharmacological treatment of HRS as dialysis in the calculation of the MELD (Ungraded).

Comment

Evidence of renal dysfunction prior to LT requires a careful evaluation and the adoption of therapeutic measures to avoid post-operative renal impairment and worse outcomes. The diagnosis of reversible AKI, supported by the response to therapy and the presence of biomarkers different from creatinine levels, and its relevance in terms of transplant prioritization deserve attention and a multidisciplinary approach.

Q14. What is the relevance and management of AKI in the early post-transplant phase?

AKI is common after LT with an incidence up to 70% and about 15% of these patients require RRT immediately after LT (A).

Early post-transplant AKI has been associated with poor outcomes: reduced long-term survival, increased rates of acute rejection and infections, longer intensive care unit (ICU) stays with higher health care costs and higher rates of CKD and mortality, independently of pre-transplant renal function (A).

The prevention and early management of peri-operative AKI is of paramount importance for the improvement of long-term outcomes (2A).

The development of AKI in the early post-transplant phase is often multifactorial and recipient-donor matching, underlying and unrecognized CKD, so intra-operative and post-transplant factors should be considered (2A).

In the LT setting, special attention should be given to patients at high risk for post-LT AKI and pre-operative risk factors (age, pre-existing comorbidities, etiology of the liver disease, obesity) should be considered (2B).

In the pre-operative phase, diuretics should be used with caution and discontinued even in cases of a slight increase in sCr, nephron toxic agents (e.g., NSAIDs, aminoglycosides, contrast agents) should be avoided and albumin should be systematically administered in patients with large volume paracentesis and/or spontaneous bacterial peritonitis to reduce the risk of early AKI after LT (1A).

In the early postoperative period, the balance between fluid loss and fluid administration should be carefully monitored, especially in patients with large amounts of ascites and RRT should be considered a valid approach to avoid acidemia, uremia, fluid overload, and systemic inflammation (2A).

Comment

The risk of development of AKI during the peri-operative or post-transplant phase is increased in patients with pre-LT renal impairment. Prompt therapeutic strategies are mandatory from the operative stage and include appropriate selection of immunosuppressive drugs immediately after LT, with delayed introduction of CNIs, or minimization of CNIs, by replacing or adding to minimal dose of CNIs, with renal sparing agents such as everolimus and mofetil mychophenolate.

4. Chronic kidney disease in patients with chronic liver disease

4.1. The impact of chronic kidney disease on chronic liver disease

CKD is a very common clinical condition, involving up to 10% of the general population, and represents the final pathway shared by a wide range of renal diseases, either as the consequence of primary renal disorders or secondary to genetic causes or other systemic diseases [124]. In addition to the well-recognized occurrence of AKI in patients with CLD, it has become increasingly evident that CLD can often be complicated even with CKD.

Renal involvement in the course of the different forms of CLD is multifaceted. First, CKD can occur as a consequence of some common liver viral infectious diseases (HCV, HBV), which can induce renal involvement through immune-mediated mechanisms (membranoproliferative glomerulonephritis associated to type 2 or 3 cryoglobulinemia; membranous nephropathy) or through the induction of inflammatory or metabolic changes (diabetes mellitus) that eventually induce chronic kidney damage [125–127]. Second, CLD and particularly non-alcoholic fatty liver disease (NAFLD), which represents the prevalent cause of CLD [128], is very frequently complicated with CKD; this strong association is likely secondary to common metabolic pathogenic pathways (obesity, insulin resistance, hypertension, altered lipid metabolism, etc.) which can cause functional and organic changes in both liver and kidneys, although it has not been completely excluded that CLD per se might play some direct pathogenic role in the development of chronic renal damage, through inflammatory, metabolic and hemodynamic pathways [129–132].

The epidemiological data available on the relationship between CLD and CKD are those relating mainly to the CKD found in patients with HCV or HBV infection related CLD or in NAFLD patients.

It is known that it is possible for HCV and HBV chronic hepatitis to induce CKD either through immune-mediated mechanisms (type I membrano-prolipherative glomerulonephritis secondary to HCV associated cryoglobulinemia; immune-complex mediated membranous nephropathy associated to HBV infections) or through indirect metabolic mechanisms (HCV induced insulin resistance or diabetes). Butt et al. [127] reported that stage 3–5 CKD was significantly more prevalent in 18,002 patients with HCV infection as compared with 25,137 control subjects (HR 1.30, CI 1.23–137). In a recent metanalysis from our group [126], which included 40 eligible studies (4072,867 patients), Fabrizi et al. reported that there was a strong association between HCV infection and the incidence of CKD (HR 1.54, CI 1.26–1.87).

On the other hand, less consistent results are present on the epidemiological relationship between CKD and HBV infections. In a meta-analysis that considered all the available studies on this topic, Fabrizi et al. [133] reported that, although a positive

relationship was found between HBV infection and CKD incidence in the only 2 eligible longitudinal studies, no evidence for a significantly increased prevalence of CKD in HBV infected patients was found by an analysis of the 7 eligible published studies. However, a recent study, performed on an Asiatic population, described a significant association between HBV infection and CKD incidence [134].

More abundant data are now available on the epidemiological links between CKD and NAFLD. However, the reported estimation of the incidence and prevalence of CKD in NAFLD patients is quite variable in the different reports, due to differences in the inclusion criteria, completeness of the information, ethnic distribution in the studied cohorts and many other confounders. We will limit ourselves to quoting the studies that included a relevant number of subjects.

In a wide review, Adams et al. [129] reported that many cross-sectional and population-based studies indicated that the prevalence of CKD is 2–3 fold higher in NAFLD patients than in non-NAFLD patients, ranging from 20% to 55% and from 5% to 30%, respectively.

In another observational study that included 11,695 participants of the Third National Health and Nutrition Examination Survey [130], patients with a diagnosis of NAFLD (who represented 18.6% of the overall cohort) had 11.31% prevalence of CKD; however the prevalence was greater than in subjects without NAFLD only for stage 1–3a CKD, but not for the more advanced stages.

A recent meta-analysis [131], which included 9 studies with a total of 96,595 patients, showed that patients with NAFLD had a higher incidence of CKD compared to those without NAFLD (HR 1.37), with the risk of developing CKD being higher in patients with more severe NAFLD.

The largest as yet published study is a 10-year retrospective cohort study, based on data retrieved from the Truven Health Analytic Market Scan Commercial and Medicare Supplemental databases [135], which included 262,619 newly diagnosed patients with NAFLD and 769,878 matched non-NAFLD patients. The authors reported that the incidence of stage 3–5 CKD was 8.2 per 1000 persons per year in NAFLD, compared to 5.5 in subjects without NAFLD.

Overall, with the exception of a study which was not able to confirm an increased incidence of CKD in NAFLD patients [136], most of the available data seem to uniformly suggest that both incidence and prevalence of CKD are higher in patients with CLD, with these figures being higher particularly in the more severe stages of NAFLD, namely NASH [137–139]. The frequent occurrence of CKD in CLD patients provides an increasing indication for combined liver-kidney transplantation [140]. Anyway, a cause-effect link between CLD and CKD remains to be demonstrated.

4.2. Prevalence of CLD in patients with CKD

CKD is one of the most complex clinical conditions [141], involving virtually all organs and systems of the human body. Consequently, CKD, when superimposed on any other disease, adds a burden which cannot but worsen clinical outcomes.

Although many studies addressed the problem of the prevalence and incidence of CKD in CLD patients showing an increased occurrence of renal complications in liver patients [137], scanty information is available on the impact of CKD on the clinical outcome in CLD patients [130].

Anyway, a possible negative impact of CKD when it complicates the course of CLD, can be readily anticipated, due to the expected contribution of CKD on increasing cardiovascular (CV) and metabolic risk factors, secondary to the retention of a high number of uremic toxins, increasing the levels of many pro-inflammatory and oxidative mediators, inducing intestinal microbiota dysbiosis, altering the control of electrolyte levels, and, not least, modifying the drug disposal which may strongly affect the therapeutic handling of CLD patients [142–145].

At variance with the many studies that addressed the prevalence of CKD in CLD, the available information on the reciprocal condition (i.e. the prevalence of CLD in CKD patients) is very limited and mostly restricted to the prevalence of HCV or HBV infection in patients on dialysis treatment. In a recent revision of the available studies on this topic, we reported that the prevalence of HCV positivity in hemodialysis patients ranges from 4.7% to 41.9% in developing countries, while it has been found to be between 1.4 and 28.3% in patients from the developed world [146]. Only a few single-center studies, conducted on small cohorts, reported that the prevalence of HCV positivity in pre-dialysis CKD patients ranges from 6.25% to 16.5% [147,148]. As anticipated, limited evidence has been produced on the prevalence of NAFLD in CKD patients. In a study from the UK, NAFLD, assessed by liver US, was reported in 17.9% of 1148 patients with an estimated GFR < 60 mL/min, not on renal replacement therapy [149]. Another study conducted on a cohort of 1525 South Korean patients with 3–4 stage CKD, reported a NAFLD prevalence of 40.9% [150].

4.3. The impact of liver disease on chronic kidney disease

Although the rationale for a potential negative impact of CLD, and in particular of NAFLD, on the clinical outcomes in CKD patients is strong [151], the available evidence is relatively limited.

In a retrospective study, about half of 261 patients with type 1 diabetes mellitus (DM), who were followed for a mean period of 5.2 years, had a diagnosis of NAFLD based on ultrasound assessment [152]. During the observation period, 61 patients developed an incident CKD and the presence of NAFLD was associated not only with a higher incidence of CKD, but also with a faster progression of the renal disease.

In the same direction, in the above-mentioned South Korean study, the NAFLD superimposed on CKD induced a greater annual decline in eGFR than that observed in CKD patients without NAFLD [150].

In the previously quoted UK study, the presence of NAFLD in CKD patients, not on dialysis treatment, was associated with an increased risk of developing CV events, but not with increased mortality or CKD progression [149].

Overall, there is some limited and observational evidence that CLD, and in particular of NAFLD, superimposed on CKD, could play a negative role on clinical outcomes of these patients.

4.4. Clinical impact of chronic kidney disease in the liver transplant setting

4.4.1. Preoperative renal function

CKD is a frequent complication in patients with advanced liver disease who are on the LT waiting list. The prevalence of kidney dysfunction in these patient populations varies greatly, ranging from 30 to 90% [153]. Pre-transplant CKD is the main determinant of post-LT chronic kidney disease, a condition observed in up to 18% of patients 5 years after LT and significantly associated with increased mortality [154–156].

Using sCr in a very large population, Nair et al. showed that pre-transplant renal dysfunction was associated with a decrease in 2-year survival after LT [157]. Asrani et al. recently showed that, among 31,289 HCV negative adult transplant recipients, those who were on hemodialysis or with a creatinine ≥ 1.5 mg/dl at the time of transplant exhibited a significant morbidity and mortality within five years after LT [158]. The magnitude of pre-transplant renal dysfunction impact on the outcome of LT is mirrored by

the concomitant presence of various unavoidable highly prevalent chronic conditions, i.e. diabetes, glomerulosclerosis, IgA nephropathy, blood hypertension. Moreover, significant hemodynamic changes and hypotension may occur during transplantation leading to a marginal chance of recovery.

4.4.2. Immunosuppression

Both donors and recipients are increasingly advanced in age; NAFLD and the individual metabolic factors are growingly represented and MELD based allocation system, which is heavily influenced by sCr, favors recipients with renal dysfunction. Calcineurin inhibitors (CNI), the cornerstone of immunosuppression in organ transplant, are associated to an increased incidence of renal damage through vasoconstrictions of the glomerular afferent arteriole, reduction in renal perfusion and then of glomerular filtration [159].

Since CNI therapy is almost universal after LT, few studies have been able to assess its clinical impact on CKD rate. In the multicenter retrospective ICEBERG study, among 402 adult LT patients the risk of chronic renal dysfunction was more than two-fold higher in the 368 CNI-treated patients vs. the 64 CNI free patients (hazard ratio [HR] 2.31; 95% CI 1.05, 5.07; $p = 0.037$) [160]. A study of 57 pediatric liver transplants found that the cyclosporine trough concentration was a significant time-dependent predictor for development of stage $\geq$ 3 CKD [161]. High CNI exposure has also been shown to increase the risk of AKI after LT by more than two-fold [162]. In a 24-month prospective, randomized, multicenter, open-label study which randomized de novo LT patients to three immunosuppressive arms (everolimus+reduced tacrolimus, TAC Control or TAC Elimination), Saliba et al. demonstrated a clinically relevant renal benefit in the 245 patients in the everolimus+reduced tacrolimus arms with the adjusted change in eGFR after 24 months of 6.7 mL/min/1.73 m^2. Thus, early introduction of everolimus with reduced-exposure tacrolimus at 1 month after LT provided a significant and clinically relevant benefit for renal function at 2 years post-transplant [163].

All together these data support the adoption of renal tailored immunosuppressive strategies. Some studies explored various CNI-minimization regimens (delayed CNI initiation, reduced CNI exposure, CNI withdrawal) but some immunological concerns have arisen. The association of a "CNI tailored regimen" to an induction therapy with an IL-2 antagonist receptor, association with mycophenolic acid or an early everolimus based CNI-free immunosuppression seems to improve renal function after transplantation [164–166].

4.4.3. Metabolic syndrome

Metabolic syndrome (MetS) is a cluster of clinical, metabolic and biochemical abnormalities comprising central adiposity, hypertension, insulin resistance and dyslipidemias. The presence of these MetS-related features significantly increase the risk of type 2 diabetes mellitus, adverse cardiac events, NAFLD and stroke. NAFLD is now recognized as the most common form of CLD in developed countries, affecting up to 25% of the population in many countries [167]. NASH is the most severe part of the disease spectrum with the potential to progress to cirrhosis and HCC. NASH related cirrhosis with or without HCC is the most growing indication for LT in the US (from 1.2% in 2001 to 9.7% in 2009) as well as in Nordic Countries [168,169]. Accumulating evidence also supports an association between MetS and CKD [170].

The prevalence of CKD in the general population is estimated to be approximately 7% [171]. The prevalence of CKD in NAFLD ranges in different studies between 20% and 55%, possibly higher in patients with more advanced liver disease [172]. The association between NAFLD and CKD is well-recognized, notwithstanding data on clinical impact being sparse and not clearly proven [149]. Conversely, the association between NAFLD, CKD and cardiovascular disease (CVD) has been of increasing interest in recent years. In fact, NAFLD and CKD have been shown to be independent risk factors associated with CVD [173,174]. This association is of huge importance in the LT setting as CVD are important contributors to morbidity and mortality during and immediately after LT as well as in the long-term follow-up [129]. Patel et al. evaluated a composite cardiovascular outcome including myocardial infarction (MI), cardiac arrest, stroke, cardiac death, heart failure or arrhythmia occurring within 4 weeks after LT in 283 LT recipients who had a coronary angiography prior to LT. In multiple regression modeling, diabetes, the key player in MetS, NAFLD and CKD, was the only factor associated with the likelihood of having a cardiovascular event [OR 2.62, 95% CI (1.49, 4.64), $p<0.001$] [175]. Due to a small sample size, they were unable to evaluate the interplay between NASH, CAD and cardiovascular outcomes at the time of LT but bearing in mind the emerging epidemiological trends of these conditions, an increasing impact could be expected across all stages of the LT process [176,177].

Questions

Q15. To what extent does the presence of CKD impact on the prognosis of liver diseases?

- The incidence and prevalence of CKD is high in patients with CLD and especially in HCV and NAFLD patients (B).
- The association between CKD and CLD in NAFLD patients is a matter of severity being higher in patients with more advanced NAFLD, namely NASH (2B). No consistent data exist on the prognostic impact of CKD on CLD (Ungraded).

Comment

The epidemiological link between CKD and CLD relies prevalently on consistent data on HCV chronic infection. More recently, data referring to a relevant number of subjects significantly linked CKD and NAFLD. A cause-effect link between the two diseases is still lacking.

Q16. What is the prevalence of CLD in patients with CKD?

- The available epidemiological data of CLD in CKD patients are limited to the association of HCV or HBV infections mainly in dialysis patients with a prevalence ranging widely from 1.4% to 28.3% in the developed world (1A).
- Scanty data and the absence of rigorous NAFLD diagnosis, does not allow an exact definition of the prevalence of CLD in the majority of CKD patients (C).

Comment

Common shared factors between CKD and CLD in NAFLD patients (diabetes, hypertension and dyslipidemia) makes the association between these two pathologies intuitive. However, limited data exist based only on observational, retrospective or cross-sectional studies. Moreover, the diagnosis of NAFLD had been based only on ultrasound. Studies are needed to specifically address this matter.

Q18. What is the clinical impact of CKD in the liver transplant setting?

- Renal dysfunction is a highly prevalent condition before LT and is associated with a per se significant impact on 5 year survival as well as on post-transplant CKD (1A).
- CNIs, the cornerstone of immunosuppression in LT, are associated with an increased incidence of acute as well as chronic kidney dysfunction after transplantation (1A). The association of a "CNI tailored regimen" to an induction therapy with an IL-2 antagonist receptor and with mycophenolic acid or an early everolimus based CNI-free immunosuppression seems to improve renal function after transplantation (1B).
- Metabolic syndrome, through the well-recognized association between CKD and NAFLD might be reasonably regarded, via the cardiovascular risk, as a significant risk factor for morbidity and mortality in the peri- and post-operative LT setting (1B).

Comment

The occurrence of a number of complications after transplantation begin before the procedure. This is the case of CKD. The MELD allocation system, the increasing prevalence in acute on chronic liver failure among transplant candidates and the increasing NAFLD pathology as a cause of liver failure and/or HCC, makes CKD one of the main Achille's heels of LT. Early identification and management of this condition should be addressed.

5. Kidney damage according to different etiology of liver disease

5.1. NASH and chronic kidney disease

While abundant data exist on the epidemiologic links between NAFLD and CKD, no consistent data are available on either the pathogenetic or epidemiological association between NASH and CKD. Indeed, a liver biopsy is essential for the diagnosis of NASH. However, most of the studies addressing these two conditions did not comprise a liver biopsy for the stage definition of fatty liver and/or NAFLD. Alternatively, studies conducted in hepatological settings lacked precise information on renal habits. This is the case, for example, of the obeticolic trial addressing the ability of obeticolic acid to improve liver fibrosis in a well-defined population of patients with NASH and so on. Thus, apart from the data of Musso [172,178], no definite conclusion could be made about the epidemiological association between NASH and CKD. The pathogenesis of NASH involves multiple hepatic and extrahepatic hits involving adipose tissue, the gut and gastrointestinal hormones involved in the progression of NASH. Dysfunction of the adipose tissue through enhanced flow of free fatty acids and the release of adipocytokines, as well as modification of gut microbiome, finally lead to proinflammatory signals which in turn culminate in hepatocyte apoptosis, endoplasmic reticulum (ER) stress and oxidative stress. Likewise, persistent low-grade inflammation, oxidative stress and gut microbiota dysbiosis are considered hallmark features of CKD.

More precise indications are available on the management of these two conditions. NASH and CKD share many etiologic/predisposing factors such as hypertension, diabetes, dyslipidemia and obesity. It is difficult to individually analyze the single metabolic factors involved in NASH-associated CKD as, in most instances, they are present contemporarily and concur both to the liver and kidney disease and their progression. Therefore, in the specific setting of NASH associated CKD, the first management object is to start with prevention through implementation of lifestyle measures according to specific guidelines as per the general population [179].

Patients with diabetes and CKD-NASH are at high risk of CV, including coronary heart disease, stroke, peripheral vascular disease, heart failure and arrhythmia. Hypertension management mirrors the general population as well, including sodium restriction, smoking cessation, alcohol avoidance and exercise, as first line interventions. In addition to glycemic control and lifestyle interventions, blood pressure lowering, lipid lowering, and antiplatelet medications are commonly used to reduce cardiovascular risk. Blood pressure lowering also affects CKD progression. ACE-Is and ARBs are valuable blood pressure reducing agents in CKD patients. They are indicated if urinary albumin excretion is elevated and are safe to combine with most other blood pressure reducing agents. Clinically significant hyperkalemia and reductions in GFR can occur in patients receiving ACE-Is or ARBs, particularly in those who have renal-artery stenosis or reduced intravascular volume, or when these agents are used together with NSAIDs, COX-2 inhibitors, or potassium-sparing diuretics. With the exception of ARBs or ACE-Is in CKD patients with high levels of urinary albumin or protein excretion, there is no strong evidence to support the preferential use of any particular agent(s) in controlling blood pressure in CKD; Other information of value in deciding on the optimal blood pressure lowering regimen include data on drug half-life and dose adjustments in CKD stage V, which may be of help in guiding the use of blood pressure lowering drugs in advanced CKD [180].

5.1.1. NASH comorbidities and chronic kidney disease

Diabetes

According to KDIGO Guidelines on diabetes and CKD, individual glucose-lowering medications have specific benefits and risks. For example, some SGLT2 inhibitors and GLP-1 receptor agonists reduce the risk of CKD or cardiovascular events with other beneficial effects (e.g., blood pressure and weight reduction), though adverse effects (e.g., hypoglycemia, bone disease) could also vary. In CKD, the benefits and risks of intensive glycemic control in general and specific glucose-lowering drugs may vary, and some drugs require dose reductions or are contraindicated. The impact of CKD on glycemia management also differs across the spectrum of CKD severity as well as in the advanced NASH stages. Therefore, among people with diabetes and CKD, optimal glycemia targets and the preferred agents used to achieve them are not clear [181].

Obesity

Avoiding weight gain may have downstream benefits in reduction of hypertension, hyperlipidemia and diabetes, with subsequent reduction in CVD and renal dysfunction. If diet and lifestyle intervention fail, medical or surgical interventions may be sought. Effects of weight loss in NAFLD and NASH is clearly shown in a randomized controlled trial of exercise and diet intervention in non-transplant patients with NASH. Goals of diabetes care in NASH associated CKD are the same as in the general population. Some medications chosen for metabolic control may benefit NASH. ACE inhibitors, Fish oil/Omega 3, Pioglitazone and GLP-1 agonist showed benefit in improving steatosis and necroinflammatory infiltrate. Oral hypoglycemic choice may impact weight gain, depending the agent used. However, the presence to some extent of GFR reduction deserves some caution when starting pharmacological intervention and choosing the drug to treat comorbidities

should take into account drug-to-drug interaction and renal dysfunction [182].

Dyslipidemia

CKD is associated with dyslipidemia with a direct link with CVD. Robust clinical evidence in non-CKD subjects suggest that lipid lowering agents reduce CVD outcomes. Statins are the most commonly used lipid-lowering medications. The benefit in reducing cardiovascular outcomes has been demonstrated in pre-end stage CKD subjects, and in post-renal transplant subjects, while no evidence exists in dialysis patients. CKD patients are at high risk of medication-related adverse events, perhaps because of the reduced renal excretion, frequent polypharmacy and high prevalence of comorbidity in this population. Therefore, reduced doses of statins are generally recommended for patients with advanced CKD. The SHARP trial provided evidence on the efficacy and safety of lowering LDL cholesterol with the combination of ezetimibe and simvastatin among a wide range of patients with CKD. Moreover, no evidence was reported of excess risks of hepatitis [183].

5.1.2. Clinical impact of NASH in the kidney transplantation setting

NAFLD and CKD share common risk factors as metabolic syndrome, however NAFLD seems to accelerate the development and progression of CKD independently of traditional risk factors. More importantly, clinical evidence indicates that the presence and severity of nonalcoholic fatty liver disease is significantly associated with incidence and stage of CKD [172]. Nonalcoholic fatty liver disease itself may exacerbate systemic and hepatic insulin resistance, cause atherogenic dyslipidemia, and release a variety of pro-inflammatory, pro-coagulant, pro-oxidant, and pro-fibrogenic mediators that play important roles in the development and progression of CKD. This suggests that overlapping mechanisms contribute to the onset and progression of liver and kidney injury in NAFLD [172].

NASH is an emerging risk factor for liver dysfunction compared with other etiologies of cirrhosis [140,178]. In the transplant setting NASH-related cirrhosis is the most rapidly growing indication for SLKT. NASH patients have worse renal outcomes, independent of associated diabetes, after receipt of SLKT. Furthermore, SLKT recipients for NASH-related cirrhosis have a higher risk of kidney graft loss compared with patients with cirrhosis of other etiologies. Singal et al. analyzed LT performed in adults and SLKT between 2002 and 2011 reported in United Network for Organ Sharing (UNOS) database: risk of kidney graft loss was over 1.5-fold higher transplant for NASH related cirrhosis [140]. Studies are needed to examine the mechanisms of these findings and develop strategies to improve renal outcomes in SLKT recipients for NASH.

The components of metabolic syndrome, are known CV risk factors and are highly present after KT, mainly due to the use of immunosuppressive therapy. Given the fact that these disorders are strongly associated with NASH, the presence of this hepatic disease in renal transplant recipients could be a strong predictor of CVD risk.

5.2. Pathogenesis of kidney diseases associated with HBV infection

Renal disease may occur in 3–5% of patients with chronic HBV infection [184,185]. Various mechanisms have been implicated in the impact of HBV infection on CKD. In fact both viral and host factors are involved in pathogenesis. An association with HLA genes has been reported, denoting the impact of genetic predisposition [184].

The different morphological forms of HBV-related renal disease include membranous nephropathy, membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, IgA nephropathy, focal segmental glomerulosclerosis and polyarteritis nodosa [185].

The histological manifestations of HBV-associated renal injuries occur as a result of immune-complex GN and Ig A nephropathy or immunocomplex-related vasculitis. The immune complexes are composed of viral antigens and the antibodies that these antigens invoke in the host [184]. To demonstrate this, hepatitis B antigen-antibody complexes have been found in renal lesions via immunofluorescence microscopy [2,186].

In particular:

- In membranous nephropathy the antigen within the immune deposits may arise from three potential viral particles: HBsAg, HBcAg, or HBeAg [185,186]. HBeAg is the one mainly involved in HBV-related membranous nephropathy. Approximately 90% of patients with chronic HBV and biopsy-proven membranous nephropathy have detectable HBeAg isolated from the glomerulus and >95% of these patients have measurable circulating HBeAg. HBeAg associates with IgG (immune complex) are in both the circulation and kidney tissue. In addition, the deposits may form from either deposition of an IgG immune complex with one or more of the stated antigens or with the de novo formation of an immune complex after deposition of the circulating antigen in the basement membrane first, followed afterward by deposition of the circulating antibody. The size and charge of the antigens are an important determinant of their pathogenicity and ability to traverse across the glomerular basement membrane. In fact, HBeAg is the smallest of the three antigens and IgG-HBeAg complexes tend to settle in the subepithelial space [2,184–186].
- Membranoproliferative glomerulonephritis is characterized by the deposition of immune complexes in the mesangium and subendothelial spaces. In patients with HBV-associated mesangial proliferative glomerulonephritis, glomerular deposition of immunoglobulin G (IgG), complement C3, and HBsAg have been reported, with a predominant deposition of IgA in the renal mesangium [185,186]. Moreover liver disease may be mild or even absent in those patients [186].
- In polyarteritis nodosa circulating antigen-antibody complexes aggregate in the vessels. It is a vasculitis affecting medium-sized arteries in most cases, which usually occurs within 4 months of HBV infection [2].

Unlike other viral-associated glomerulonephritis, HBV-induced immune complex disease occurs after a prolonged carrier state [185].

Renal injury caused by HBV may be related to immune reactions, with glomerular deposition of immune complexes but also virus-induced specific immunological effector mechanisms (specific T lymphocyte or antibody). Such reactions may damage the kidney or have indirect effects from virus-induced cytokines/mediators on renal tissue, also inducing apoptotic damage in the renal tubular cells [133,184,187]. HBV antigens (HBsAg, HBcAg and HBeAg) are also expressed in renal tubular epithelial cells. They can upregulate complement-mediated inflammatory gene pathways and contribute to the pathogenesis of nephropathya. Furthermore, in chronic HBV infection, steatosis may be present and could induce lipid peroxidation and increase plasma inflammatory biomarkers.

However only a small percentage of patients develop renal disease: this suggests concomitant factors are necessary (such as genetic susceptibility, cell-mediated immunity abnormalities, and or environmental conditions) to develop renal disease [133].

5.2.1. Burden of HBV infection in patients on dialysis

Epidemiology

Control of HBV infection was one of the major advances in hemodialysis patients, in particular for those awaiting KT [188].

Infection with HBV appeared one of the main health problems in hemodialysis since the introduction of the dialysis technique, which occurred in the 1960s; the Australia antigen, later renamed HBsAg, was discovered by Blumberg in 1965 [189,190]

The first epidemiological studies from the US published in the 1970s revealed an incidence of 3–6% new cases in hemodialysis, with a prevalence of 8% [191]; the incidence and prevalence subsequently fell sharply, to 0.5% and 3.8% in the 1980s and to 0.05% and 0.9% in the 2000s respectively [192].

This improvement was mainly correlated to four factors:

- introduction of the screening test for HBsAg in blood donors
- introduction, in 1977, of dedicated hemodialysis machines in HBsAg carriers
- introduction of the HBV vaccine in 1982
- introduction of erythropoietin in 1986

The DOPPS study (Dialysis Outcomes and Practice Patterns Study) results published in 2003 reported that the prevalence rates of chronic HBV infection on regular dialysis ranged between 0% and 7%; among these, Italy had the highest prevalence [193].

Natural History

The natural history of HBV infection in the hemodialysis population is characterized by usually asymptomatic evolution during the acute episode and a very high chronicization rate (more than 60%) linked to the global state of immunosuppression in hemodialysis patients. The frequent features of normal transaminase levels in patients with active HBV infection is due to low levels of pyridoxine and increased viral clearance by hemodialysis; moreover, the reduced cytolytic response related to uremia-induced immunosuppression contributes to extremely low levels of hepatic enzymes.

Available data on the natural history of HBV infection in hemodialysis are scarce and poorly characterized because chronic HBV usually progresses slowly; in contrast, life expectancy of hemodialyzed patients are significantly shorter than in the general population due to cardiovascular diseases and sepsis; a study conducted in 2008 on a cohort of 403 hemodialyzed patients showed a significant increase in mortality only in patients who were HBsAg positive with advanced liver disease (194).

Cirrhosis is not frequent in dialysis patients but carries a higher mortality rate than in the general population [194].

Therapy

Since the 1990s, the introduction of antiviral therapy with nucleoside analogues (lamivudine, emtricitabine, telbivudine and entecavir) and nucleotide analogues (tenofovir and adefovir) has deeply changed the natural history of hemodialysis patients and those awaiting renal transplantation with HBV infection.

Antiviral therapy in this population has clearly improved survival; a study conducted in 2014 showed that HBsAg-treated positive patients had a 10-year survival comparable to negative HBsAg controls (39.1% vs. 33.2% $p = 0.12$ and that the suppression of viral replication was associated with a significant increase in survival (HBV DNA ⟨2 log10 IU / mL, 90.9% vs. HBV DNA⟩ 2 log10 IU / mL 74.1% at 5 years $p = 0.049$). The study confirmed that mortality due to liver causes in the hemodialysis population is infrequent, as the cardiovascular and infectious causes occur earlier with respect to the progression of liver disease [195].

5.2.2. Evaluation of HBV candidates for kidney transplant

Antiviral treatment with analogues in HBV cirrhosis patients has significantly reduced the indication for liver transplantation, while HCC chemo-prevention by long-term administration of entecavir (ETV) or tenofovir disoproxil fumarate (TDF) is still a matter of debate.

In cirrhotic patients treated with ETV or TDF the annual incidence of HCC was 2.6% and 3.7%, comparable to that of HBV untreated patients [196,197].

Because early diagnosis of HCC allows curative therapies, close surveillance for HCC risk is of strategic importance also in cirrhotic patients treated with high genetic barrier antivirals.

HCC development is the only factor affecting liver-related mortality in HBV patients under NUC and HCC is the main indication for LT even in combined liver-kidney transplant candidates.

Isolated KT in patients with compensated cirrhosis is still a debated option because of the potential risk of post-operative decompensation and the potential increased risk of HCC related to immunosuppressive therapy. The Asian study published on a 2015 Korean series of 12 patients with HBV-related cirrhosis related to an isolated and transplanted antiviral treatment found that survival in this group was similar to that of HBV patients without cirrhosis. The incidence of HCC was very high but not significantly different from non-cirrhotic patients (33% vs. 25%) [198].

5.2.3. Evaluation of HBV kidney transplanted patients

Frequency of HBV infection in KT patients is 20% in Italian series with different prevalence in different regions. After transplant, the natural history of HBV infection changes and accelerates and, consequently, mortality for liver diseases increases.

A study published in 1996 in the pre-antiviral era revealed a rapid histological progression after KT. While before transplantation about 40% had no signs of liver disease, only 6% maintained a normal histology afterwards and 28% of patients had histological progression to cirrhosis. Following studies on transplanted patients followed for over 10 years showed a significant reduction in survival in HBsAg+ patients [199].

For many years before analogues therapy HBV infection was considered a relative contraindication to KT due to high liver-related mortality; however, the introduction of antiviral therapy has completely changed the prognosis of KT with HBV infection.

Patient survival has significantly increased since 1986 after the introduction of antiviral therapy; a study published in 2010 documented an 81% survival at 10 years in patients who received treatment with analogues. However, liver failure is still the leading cause of death for this cohort. The most recent KDIGO and EASL guidelines state that screening for HBV infection must be performed in all hemodialysis and transplant evaluation patients and all HBsAg transplant-positive subjects should receive antiviral treatment with ETV or TAF regardless of the level of viral replication. Lamivudine is not recommended because of the high risk of resistance. NA prophylaxis and treatment should be continued long-term. In patients with significant fibrosis or cirrhosis, close surveillance for HCC with six-month ultrasounds and AFP dosage is strongly advised [200].

5.3. Pathogenesis of renal diseases associated with HCV infection

HCV infection in CKD stage 5 patients is more frequent than in the general population. The rate of anti-HCV seropositive dialyzed patients ranges between 1% and 40% [3,201]. The risk of HCV infection increases with the number of years on hemodialysis. The main

reason seems to be patient-to-patient transmission due to unsatisfactory compliance with standard/specific infection control practices. In fact, hands blood contamination among staff members or medications, devices and equipment contamination can contribute to HCV transmission, while the use of a dedicated dialysis machine does not confer protection against transmission [3,201,202]. Because of an increased risk of HCV infection in a hemodialysis setting, the recent international guidelines recommend screening all patients upon initiation of in-center hemodialysis [201].

The risk of HCV infection among patients who receive peritoneal dialysis or home hemodialysis has not been quantified. The need for in-center hemodialysis during the course of the disease will put these patients at risk of acquiring HCV infection comparable to other dialyzed patients. Therefore, since these patients transiently receive in-center hemodialysis, they should undergo HCV infection screening upon initiation of home or peritoneal dialysis to document baseline HCV infection status, and the case for interim in-center hemodialysis [3].

5.3.1. Screening of HCV in patients on dialysis

HCV infections are mostly asymptomatic, making screening necessary to detect infection in high-risk populations, particularly in hemodialysis patients in whom signs or symptoms of acute HCV infection are rarely recognized. However, blood testing for ALT has weak diagnostic value in renal patients as levels most commonly fall within the lower limit of normal range, but if an unexplained elevation of ALT occurs, the patient should be tested for HCV infection. The reason for this phenomenon is unclear and various agents could be involved: vitamin B6 deficiency, uremic toxins accumulation and malnutrition, making the ALT levels monitoring only a low value test [203].

The KDIGO HCV Work Group suggests that in hemodialysis units initial HCV testing by enzyme immunoassay (EIA) should be considered, since third-generation EIAs have high sensitivity (98.8%) and specificity (100%) [201]. However, the time between HCV infection and the appearance of detectable antibodies (serological window period) is generally more than 40 days using third-generation EIAs [204]. Fourth-generation EIA is the most commonly used screening tool for HCV infection and allows the HCV antibody to be detected significantly earlier than the other assays [3,201,205].

If positive, immunoassay must be followed by nucleic acid testing (NAT). Initial testing with NAT should be considered in high prevalence units because anti-HCV test can be false-negative: immune-compromised patients might either exhibit a delay in antibody production or an absence of specific antibodies following acute HCV infection.

Samples collected to test for HCV by NAT should be drawn before dialysis, because hemodialysis sessions reduce viremia levels, although the mechanism remains unclear.

An anti-HCV–negative, HCV RNA–positive (i.e., NAT-positive) profile strongly suggests acute HCV infection.

A positive anti-HCV antibody test may indicate either current infection or resolved past infection. The Center for Disease Control and Prevention (CDC) updated guidelines for hepatitis C testing recommend that a positive anti-HCV antibody result should always be followed up by testing for the presence of HCV RNA with an FDA-approved NAT to identify subjects with an active HCV infection.

NATs can detect HCV RNA as early as 1 week after exposure and detect all infected cases by 2–3 weeks post-exposure. Currently, available HCV NATs are highly sensitive, detecting as little as 5 IU/mL of HCV RNA, and highly specific (99%) [205,206].

Repeat anti-HCV testing is recommended every 6 months in hemodialysis patients who are not infected with HCV (anti-HCV antibody negative).

Hemodialysis patients with sexual behavior at risk should be screened more frequently.

Patients with resolved infection (HCV-RNA negative and HCV-Ab positive) require periodic screening (every six months) for the re-infection risk.

When a new infection is identified in an HD unit, all NAT negative patients should be tested [3,201,202].

5.3.2. Treatment of HCV in patients on dialysis

Effective treatment regimens are now available for HCV-infected hemodialysis patients identified as HCV RNA positive.

According to international guidelines, all patients with CKD and HCV infection should be considered for treatment with direct acting antivirals (DAAs), prioritizing those with symptomatic cryoglobulinemic vasculitis, extensive liver fibrosis and stage 4–5 CKD [207–210]. Appropriate timing and choice of antiviral therapy must be individualized to each patient according to comorbidities and transplant candidacy.

Treatment of patients with chronic hepatitis C with or without cirrhosis and renal impairment, including hemodialysis patients, is identified by the Italian National Health System (INHS) as 10 AIFA criteria (Fig 1).

According to the EASL and AISF guidelines [208,209], the regimens currently available for patients with impaired renal function are:

- Pangenotypic combinations: glecaprevir (PI) plus pibrentasvir (NS5A inhibitor) for 8 or 12 weeks, according to the general recommendations.
- Genotype-specific regimens: grazoprevir (PI) and elbasvir (NS5A inhibitor) only for genotype 1 and 4. In particular, genotype 1a and treatment- naiv̈e patients infected with genotype 4 with an HCV RNA level $\leq$800,000 IU/mL (5.9 Log10 IU/mL) can be treated with the combination of grazoprevir and elbasvir for 12 weeks.

Clinical trials and real-life data clearly showed that regimens based on DAA are safe and without significant side effects also in HD patients, although it is necessary to carefully follow patients treated with ribavirin and/or those with advanced liver and/or kidney disease.

In patients on hemodialysis, a non-sofosbuvir based regimen should be preferred whenever possible [209].

The predominant circulating metabolite of sofosbuvir, GS-331,007, is cleared renally and accumulates in patients with severe renal impairment or ESRD, but dosing recommendations for patients with ESRD are not available at the moment. However, real-world case series in patients with ESRD undergoing dialysis demonstrate substantial use of sofosbuvir-based regimens in this population, with no safety concerns identified [211].

EASL guidelines conclude that sofosbuvir should be used with caution in patients with end-stage renal disease, only if an alternative treatment is not available, since no dose recommendation can currently be given for these patients [209].

5.3.3. Treatment of HCV-positive candidates for kidney transplant

As stated above, effective and safe antiviral treatment regimens are currently available for HCV-infected patients through all CKD stages and also for KT recipients. Indeed, a strong advocacy for potential complete HCV eradication while on the waiting-list was built up as soon as DAAs had been licensed. The possibility of achieving this goal before transplantation had been considered more relevant in view of the potential interference with antirejection drugs and renal safety after KT. However, the fragile hemodialysis population, the core of KT candidates, is affected by multiple comorbidities, and, even if HCV infection has been shown to be a strong, consistent and independent risk factor for

all-cause (RR 1.35, 95% CI 1.25–1.47), liver-related (RR 3.82, 95% CI 1.92–7.61), infectious (RR 1.53, 95% CI 1.11–2.12) and cardiovascular (RR 1.26, 95%CI 1.10–1.45) mortality [212], nevertheless, a mortality rate as high as 15–20%/year, mainly due to cardiovascular risk, overcomes the benefit of HCV eradication on survival.

A second and more relevant issue when advising HCV treatment before KT are the implications relating to patients' access to the transplant waiting-list. KT is the most successful intervention for end-stage kidney disease, and people on hemodialysis who achieve KT experience a substantial survival advantage. Achieving exclusively SVR in HCV+ hemodialysis patients may therefore pose a significant survival disadvantage, should it preclude them from accessing specific KT programs, such as those which transplant kidneys from HCV+ donors. These programs have been clearly shown to offer an advantage to patients considering their ability to receive a transplant in a significantly shorter period of time [213]. Consistent safety data of HCV eradication also in the post-transplant period suggests the possibility that treatment could be postponed after transplant, if HCV+ donor KT is available, thus reducing waiting time and shortening dialysis period [214].

5.4. Alcohol-related liver disease and kidney injury

Renal failure with or without structural renal damage is frequently associated to alcohol abuse; chronic alcohol consumption is a well-known risk factor for tissue injury.

Alcoholic kidney injury may be associated with ethanol-induced oxidative and inflammatory stress; moreover, the relationship between the kidney and other organs, in particular the liver and intestine, may be involved in kidney damage.

Alcohol induces expression of the microsomal ethanol oxidation system (CYP2E1) particularly in the kidney, producing reactive oxygen species resulting in oxidative stress that damages cell membrane phospholipids and recruitment of neutrophils [215].

Other studies suggested that ethanol can increase the expression of other two nitric oxide synthetases, enhancing nitric oxide production that triggers tissue damage [216].

Several studies have established a central role of glomerular damage with mesangial deposition of immunocomplex-IgA in determining renal failure [217]. Specifically, histopathological studies showed that about 70% of patients with alcoholic cirrhosis showed glomerular changes, with IgA mesangial infiltrate in about 90% of cases [218,219].

From a physiopathological point of view, IgA alcoholic nephropathy has been classified among the secondary forms of IgA nephropathy due both to hypersecretion of IgA complexes probably mediated by mucosal damage with increased intestinal permeability and reduced hepatic clearance of immunocomplexes by hepatocytes [220].

The kidney is particularly sensitive to an increased IgA load. In fact, IgA glomerulonephritisis is one of the most frequent forms of primary glomerulonephritis.

Although IgA mediated mesangial damage is frequent in these patients, only a low percentage of proved glomerulonephritis is associated with renal insufficiency. In particular, the correlation between alcoholic cirrhosis severity and development of chronic renal failure has not been defined; portal hypertension severity and the extent of portal-systemic shunts are among the principal precipitating risk factors [221].

IgA nephropathy in patients with liver cirrhosis can occur early with microhematuria, more rarely with proteinuria and alteration of serum creatinine. Circulating IgA levels can be increased and urine test alterations have been shown to correlate with the extent of mesangial damage. The diagnosis is essentially clinical, since a renal biopsy, which is the gold standard in the diagnosis of IgA related nephropathies, is not adopted in current clinical practice in these patients, due both to the risks of the procedure and the low prognostic impact.

In addition, there is no specific etiological treatment for this nephropathy, whose prognosis often depends on the evolution of liver disease. The regression of mesangial damage following abstinence, LT or following interventions to reduce portal hypertension is anecdotal [222].

5.4.1. Clinical impact of AKI in acute alcoholic hepatitis

Renal damage is a frequent complication during acute alcoholic hepatitis and is often an early sign of multi-organ failure (MOF). AKI in acute alcoholic hepatitis is determined by hemodynamic disorders, infections, use of nephrotoxic agents and hyperbilirubinemia, which has been shown to contribute to the development of acute tubular damage rather than by direct cytotoxic alcohol damage [223].

The risk of AKI in alcoholic hepatitis was recently analyzed in a prospective cohort study on 773 patients hospitalized for severe alcoholic hepatitis.

In this study 32% of patients developed AKI during hospitalization; hepatic encephalopathy, SIRS, and MELD score at admission were found to be predictors of AKI [224].

Appearance of AKI occurs early in acute alcoholic hepatitis and is strictly related to mortality. In a recent study the 90-day mortality rate for patients with alcoholic hepatitis and AKI was 65% vs. 7% for patients who did not have AKI [225].

Therefore, in acute alcoholic hepatitis, the immediate removal of causes of worsening renal function is strongly suggested. It is essential to modulate diuretic therapy and adapt hydration, identify early and treat with adequate antibiotic therapy for infections and suspend any nephrotoxic agents.

A recent study has also highlighted how the use of non-selective beta-blockers during acute alcoholic hepatitis is independently associated with the development of AKI; therefore their suspension could be indicated [226].

In the absence of clinical improvement, temporary renal replacement therapy is indicated, which however does not guarantee the restoration of renal function, but can contribute to its recovery [227].

5.5. Indications for isolated liver or combined liver-kidney transplantation

The introduction in 2002 of MELD as a tool to address risk criteria for liver graft allocation and prioritization led to an increase of LT recipients with renal damage, the proportion necessitating hemodialysis 6 months after transplant growing from 2% to 5% of patients and to an unexpectedly and dramatic increase of combined SLKT [228,229]. In the USA the number of SLKT dramatically increased from 135 to 731 in 2000 and 2016, respectively [230]. This procedure was carried out without formal guidelines which in turn resulted in a great variability between centers in respect to indication while outcomes in terms of transplant benefit had not been clearly defined [231].

In a preliminary matched control analysis between patients who had undergone kidney alone, liver alone or combined liver-kidney transplant, no benefit in the SLKT cohort was found despite the allocation of higher quality grafts [232]. This series included patients with more advanced liver disease and with AKI, thus also at high risk for liver transplant alone. First data addressing a rule for SLKT identified a more than 3-months dialysis need before transplant as a positive predictive factor for better outcome in the combined SLKT vs. liver transplant alone. Hmoud et al. analyzed data of 3549 patients listed for SLKT in 2015. Among them, 422 (12%) received an isolated LT. Overall survival was poorer in the isolated LT and 24% needed a renal transplant within

Table 3
Parameters for liver function evaluation in patients with renal failure.

Biochemical parameters	Score	Ultrasound	Hemodynamics	Clinical	Fibrosis Score (only for HCV)
Platelets Bilirubin Albumin	MELD CHILD-PUGH	Caudate lobe hypertrophy Enlarged spleen Spleno-portal axis dilation Fibroscan	HVPG Varices	Ascites EPS	FIB-4/APRI

MELD: creatinine, INR, bilirubin.
Child-Pugh: serum bilirubin and albumin levels, prothrombin time, ascites, and encephalopathy.

1-year after LT. The proportion of patients who recovered renal function after transplantation in this study was 33% but figures between 5% and 68% are reported accounting for heterogeneous patients characteristics [232]. All together, these data claimed the need for guidelines for patient selection. An issue in SLKT is the lack of defined predictive factors of functional renal recovery and the futility risk in patients with intermediate MELD which prompted in the main transplant organization (UNOS and Eurotransplan) the adoption of delayed KT in those LT recipients not recovering renal function within 1-year after LT, namely a "safety net" with the opportunity for an additional score [233].

5.5.1. NASH associated liver disease

In view of the emerging epidemic association between NASH and CKD, both comprising diabetes and hypertension as main clinical features, an increasing need for SLKT can be presumed. Singal et al. analyzed more than 13,000 transplant recipients and found MELD score to predict SLKT in those with diabetes and hypertension [1.02 (1.01–1.03)]. The analysis identified a MELD score $\geq$ 43 for a better 5-year survival after SLKT while in patients with MELD score $\leq$ 29 SLKT was beneficial compared to isolated LT only in those with sCr $\geq$ 2 [73% vs. 76%, $p = 0.32$; 0.85 (0.60–1.2)]. Thus, in patients with diabetes and hypertension, the main stigmata of NASH, creatinine and MELD, seem able to stratify risk and address indication [234].

5.5.2. HBV chronic liver disease

Despite its decreasing rates, especially in developed countries, HBV positive patients pose relevant challenges in the setting of SLKT and require a strict collaboration between nephrologists and gastroenterologists. A typical scenario is an HBsAg positive patient who, according to EASL guidelines, should receive anti-HBV prophylaxis or treatment with NA. Historically, ETV is the preferred option in HBV naïve patients but, the recent availability of TAF could allow a safer prophylaxis or treatment in a fragile renal population like SLKT patients. Very recently, Sripongpun et al. assessed the impact of switching LT recipients to TAF, demonstrating its safety together with a trend toward improvement in renal function [235]. These data suggest that in SLKT recipients, in whom preservation of liver and renal function is critical, TAF is an important component in optimizing their long-term outcome.

5.5.3. HCV chronic liver disease

HCV CLD has a definite cure represented by the availability of direct acting antivirals which led, during last 5 years, to the eradication of most of the known infected cases. MELD score in patients with both liver and kidney dysfunction could not be an adequate measure to stratify liver disease risks as creatinine, an important variable in the score, tends to overestimate the severity of liver disease. Therefore, in this specific context of SLKT, other liver severity parameters must be strictly evaluated and, especially, portal hypertension. Portal hypertension is the capital hallmark of liver cirrhosis. It is associated to a significant morbidity and mortality rate and the best tool in defining prognosis of cirrhosis. The hepatic venous portal gradient (HVPG) is the gold standard to assess portal hypertension and the best predictor of esophageal varices and clinical cirrhotic events of decompensation (ascites, encephalopathy and variceal bleeding). An HVPG $>$ 10 and $>$12 mmHg, namely clinically significant portal hypertension, is able to identify patients at risk of developing varices and clinical decompensation, respectively [236]. Although the routine application of HVPG measurements is limited by its invasiveness, it should nevertheless be favored in a multidisciplinary setting when managing transplant resources. Transient elastography (TE) is a non-invasive method to assess liver fibrosis which has been demonstrated in various settings and demonstrated to adequately correlate with HVPG. A recent systematic review of 8 studies including 1356 patients demonstrated that TE is able to identify clinically significant portal hypertension with high accuracy and correlation.

The presence of clinically significant portal hypertension has been associated to an increased surgical risk in several non-transplant surgical settings [237,238]. A summary of risk parameters able to stratify liver function and useful to address a proper indication to SLKT are reported in Tables 3 and 4.

Table 4
Criteria for simultaneous liver-kidney transplant.

Patients categories	Risk criteria
Compensated cirrhosis	Presence of esophageal varices HVPG $\geq$ 10 mmHg Active liver disease (alcohol, NASH) HCC *Liver Stiffness $\geq$ 30 and PLT $<$ 110.000 Previuos decompensation
Decompensated cirrhosis	Ever

Questions

Q19. What is the prevalence of NASH in CKD?

- At this time the prevalence of NASH in patients with CKD is not clearly defined (Ungraded).

Comment

Studies are needed including liver histology and accurate staging of renal damage before drawing any conclusion.

Q20. What is the suggested pathogenetic link between NASH and CKD?

- The dysfunction of adipose tissue, systemic inflammation and modification of the gut microbiome are the common pathogenetic mechanisms in NASH and CKD (1B).
- The interrelation of these mechanisms in the presence of both deserves specific studies. (Ungraded)

Comment

NASH and CKD share many epidemiologic and pathogenetic links, but studies specifically addressing these pathologies need further consistent data.

Q21. Is the natural history of NASH-related CKD different from other etiologies of kidney damage?

The lack of consistent epidemiological studies and the absence of focused pathogenetic data on NASH associated CKD do not allow any definite conclusion (Ungraded).

Comment

Overall, apart from the epidemiological association between NASH and CKD, the pathogenetic links and data on natural history are lacking.

Q22. How should comorbidities be managed in NASH associated CKD?

The management of NASH associated CKD relies on proper identification and management of risk factors (hypertension, diabetes, dyslipidemia and obesity) (1B).

In view of the per se' high cardiovascular risk in CKD patients, strict glycemic control, treatment of hypertension, and lifestyle modification aimed at weight loss, physical activity and smoking cessation, should be vigorously promoted in NASH-associated CKD (1A).

Comment

Metabolic comorbidities in NASH associated CKD must be managed and controlled in a vigorous way by a multidisciplinary intervention and counseling in view of the increased cardiovascular and oncologic risks.

Q23. What is the clinical impact of NASH in the setting of kidney transplanted patients?

The presence of NASH in renal transplant recipients could be a strong predictor of CVD risk (1C).

Studies are needed to understand the clinical impact of NASH in the setting of kidney transplanted patients (Ungraded).

In the transplant setting NASH-related cirrhosis is the most rapidly growing indication for SLKT (1B).

Q24. What is the pathogenesis of kidney diseases associated with HBV infection?

(a) Various mechanisms have been implicated in the impact of HBV infection on chronic kidney disease. Both viral and host factors seem to be involved in the pathogenesis (Ungraded).
(b) The histological manifestations of HBV-associated renal injuries occur as a result of immune-complex GN and Ig A nephropathy or immunocomplex-related vasculitis (1B).

Comment

HBV infection is one of the major public health problems worldwide. The demonstrated link between HBV hepatitis and kidney diseases, adds arguments to the growing body of evidence suggesting that chronic HBV infection may be a contributor to the increasing incidence of CKD

Q25. What is the burden of HBV infection in patients on dialysis?

- Prevalence rates of chronic HBV infection on regular dialysis ranges between 0% and 7%; among these, Italy has the highest prevalence (1A).
- HBV infection in hemodialysis is characterized by a significant increase in mortality only in HBsAg positive patients with advanced liver disease, cirrhosis is not frequent in dialysis patients but is loaded by a higher mortality than in the general population (1B).
- Antiviral therapy with nucleoside and nucleotide analogues has strongly increased survival in patients with HBV infection in hemodialysis and those awaiting renal transplantation (1A).
- Since HCC is the main indication for LT in HBV cirrhotic patients even in combined liver-kidney transplant candidates, close surveillance for HCC risk is strongly advised in patients with advanced fibrosis stage and cirrhosis (1A).
- Isolated KT in patients with compensated cirrhosis is still a debated option because of the potential risk of post-operative decompensation and the potential increased risk of HCC related to immunosuppressive therapy (2B).
- The nucleos(t)ide analogues which have a high barrier to drug resistance (tenofovir or entecavir) has improved survival in HBV kidney recipients significantly, however, liver failure and HCC is still the leading cause of death for this cohort (2B).

Comment

Overall, HBV infection in patients on dialysis must be regarded as a significant factor for liver disease progression and HCC, thus suggesting a strict follow-up collaboration between liver and kidney specialists.

Q26. What is the pathogenesis of renal diseases associated with HCV infection?

The pathogenesis of HCV-related nephropathy has not yet been fully clarified, but either direct mechanisms related to kidney infection or mediated by the host's immune response have been described (1B).

Comment

The role of immune complexes secondary to production and deposition of circulating cryoprecipitate is widely described [240,241]. Nevertheless, some pieces of evidence suggest an involvement of the direct infection of cells (renal and/or lymphatic).

Q27. What is the clinical impact of renal diseases associated with HCV infection?

A strong association had been reported between HCV infection and the incidence of CKD (1A).

The association with a more advanced CKD stage could be related to the involvement of immune mediated mechanism and/or indirect metabolic mechanisms (2B).

Comment

Kidney involvement is frequent in HCV positive patients and includes proteinuria, different types of glomerulonephritis,

cryoglobulinemia and CKD. As it is well known that HCV infection predisposes to the onset of CKD and worsens the prognosis of renal patients by increasing the risk of ESRD in non-dialysis patients and of mortality in both non-dialysis and dialysis patients, in non-dialysis CKD patients as well as graft loss and patient mortality in kidney transplant recipients, HCV could be regarded as a significant negative prognostic factor in renal diseases

Q28. Is screening for HCV recommended in patients on dialysis?

Screening for HCV infection is recommended in all patients at the time of initial evaluation of CKD (1A).

Screening for HCV infection is recommended in all patients upon initiation of in-center hemodialysis or upon transfer from another dialysis facility or modality (1A).

Screening of HCV infection is suggested in all patients upon initiation of peritoneal dialysis or home hemodialysis (1B).

Comment

In view of the high prevalence of HCV infection in dialysis, screening of HCV is recommended on a regular basis and international rules are strongly advised.

Q29. Which test should be used for screening?

We recommend using an immunoassay followed by nucleic acid testing (NAT) if the immunoassay is positive (1A).

Screening for HCV infection with immunoassay or NAT in in-center hemodialysis patients is recommend every 6 months (1A).

In units with a new HCV infection, all NAT negative patients should be tested by NAT techniques and the frequency of subsequent HCV testing should be increased (1B).

In hemodialysis patients with resolved HCV infection repeat testing is recommended every 6 months using NAT to detect possible re-infection (1B).

Comment

Besides patients with positive immunoassay, a NAT test might be always considered especially in hemodialysis centers with a high prevalence of HCV.

Q30. Who should be treated?

All hemodialysis patients and HCV infection should be considered for treatment with direct acting antivirals (DAAs) (1A).

Patients with CKD G5D should be treated with a ribavirin-free DAA- based regimen (1A).

Comment

In view of the high efficacy and safety of available antiviral drugs, an antiviral schedule must be offered and discussed in every HCV dialysis patient aiming to improve the patient's prognosis and reduce the risk of an infected dialysis room.

Q31. In HCV-positive candidates for kidney transplant, who should be treated and how?

- HCV positive candidates for KT must be considered eligible for HCV eradication and results of DAA applications in these settings showed a good safety profile and excellent efficacy (1A).

An anticipated long waiting time or suspension of a transplant program, must expedite addressing the antiviral schedule (1A).

Renal safe regimens such as Glecaprevir/pibrentasvir or Elbasvir/grazoprevir must be preferred (1A).

The choice to defer antiviral treatment after kidney transplant should rely on an active HCV positive donors program (2B).

Q32. How does the pre-transplant work up differ in combined liver/kidney transplant in respect to the single liver or kidney one?

Apart from vascular study of the iliac compartment, no different pre-transplant work up is suggested when SLKT is planned instead of a single liver or kidney one (1B).

Third level cardiovascular assessment should be performed according to liver transplant evaluation (1A).

Comment

Cardiovascular risk could be regarded as a significant risk in patients eligible for SLKT. Thus an in-depth cardiac evaluation, especially in the case of NASH indication, is suggested.

Q33. What is the pathogenesis of kidney injury associated with alcohol misuse?

Alcoholic kidney injury may be associated with ethanol-induced oxidative and inflammatory stress; moreover, the relationship between kidney and other organs, in particular liver and intestine, may be involved in kidney damage (2C).

In chronic alcohol abuse mesangial deposition of immunocomplex-IgA plays a central role in glomerular damage and chronic kidney damage (1B).

In patients with liver cirrhosis IgA nephropathy can occur early with microhematuria, proteinuria (2B).

There is no specific etiological treatment for IgA nephropathy, the prognosis often depends on the evolution of liver disease. A regression of mesangial damage following abstinence is anecdotal (2C).

Comment

Chronic alcohol consumption is a recognized risk factor of kidney injury, through several oxidative mechanisms that trigger tissue damage. In addition, several studies have established that IgA deposition plays a central role in glomerular damage in CLDs. Natural history studies have confirmed no specific etiological treatment for IgA kidney damage, in these patients the prognosis often depends on the evolution of liver disease.

Q34. What is the clinical impact of AKI in acute alcoholic hepatitis?

AKI is a frequent complication during acute alcoholic hepatitis and is often an early sign of multi-organ failure (MOF) and strictly related to mortality; therefore, the immediate removal cause of worsening renal function is strongly suggested (1B).

Comment

Alcoholic acute hepatitis is a systemic clinical condition characterized by acute liver inflammation caused by prolonged heavy alcohol use. AKI in acute alcoholic hepatitis is determined by hemodynamic disorders, infections, use of nephrotoxic agents and hyperbilirubinemia. In this condition, AKI is a more frequent and earlier extra-hepatic organ failure and is a strong determinant of short-term prognosis. Prevention, immediate treatment and

organ support in AKI during acute alcoholic hepatitis is therefore strongly recommended.

Q35. What are the indications for isolated liver or combined liver-kidney transplantation?

Combined liver-kidney transplantation has been demonstrated to be accompanied to a patient's and graft survival advantage in the presence of IV stage CKD (eGFR < 30 mL/min) or in the presence of hemodialysis for at least 3 months before transplant (1B).

In patients with liver cirrhosis under evaluation for a combined liver-kidney transplant, MDRD-6 is the most accurate method for GRF estimation in those with a GFR 30 mL/min (1B).

The complexity of the entire process and the difficulty in a proper differential diagnosis between the various forms of renal damage associated with cirrhosis, need a final decision at multidisciplinary level among the different transplant teams involved (1).

A combined liver-kidney transplant has a better outcome in respect to liver transplant alone in case of:

- metabolic disease on a genetic background (hyperossaluria, aHUS with factor H mutation, non-neuropathic familial amyloidosis)
- liver and kidney polycystic disease
- clinically significant portal hypertension (1A).

Comment

As robust predictors of renal recovery are lacking, evidence coming from different series identified duration of renal failure as the critical point to direct clinical decision. That is, a simultaneous liver-kidney transplant had been accompanied by a patient and graft survival advantage in the presence of an eGFR ≤ 25 mL/min or haemodialysis need for at least 6 weeks in patients with AKI while in the case of CKD, 3 months duration of haemodialysis or eGFR < 30 mL/min is able to stratify patients to be addressed to a single or combined transplant.

6. Polycystic kidney and liver disease

6.1. Genetic background, phenotypic expression and natural history in polycystic kidney and liver disease

Autosomal dominant polycystic kidney disease (ADPKD) is a rare, genetic, renal tubular disease. Around 12.5 million adults in the world are affected and it is the fourth cause of kidney failure, with the need for RRT (dialysis and/or transplant [239]).

It is caused by a heterozygous mutation mainly in two genes: *PKD1*, which accounts for 80–85% of cases, *PKD2* mutated in about 15% of cases. PKD1, located at 16p13.3 codes for Polycystine 1, and PKD2, located at 4q21 codes for Polycystine 2, two membrane proteins associated with primary cilium, more than 1400 pathogenic mutations have so far been reported. Polycystine 1 is a (520 Kd) receptor protein, composed of a long extracellular domain, 11 transmembrane domains and a cytoplasmic domain. It is involved in cell-cell and cell-matrix interaction, in the down regulation of apoptosis and it is also a receptor. Polycystine 2 is instead a calcium channel regulated by voltage. The two proteins interact mediating its signal transduction [242].

In 2016, heterozygous mutations in GANAB were identified in nine families with autosomal dominant polycystic kidney or liver disease; these mutations were then found in two other families with predominant liver involvement. GANAB encodes the α subunit of glucosidase II, a resident enzyme of the endoplasmic reticulum involved in N-linked glycosylation, which is a key quality control process that governs folding, maturation and trafficking of membrane and secreted proteins [243].

Regarding ADPKD pathogenesis, it is commonly accepted that the polycystines functional loss transforms tubular epithelial cells into poorly differentiated and hyper-proliferating cells, which give rise to renal cysts. In particular, the cysts are formed as dilatation of the tubular walls, full of liquid filtered by the glomerulus leading to connections loss with the nephron [244].

ADPKD has strikingly high phenotypic variability, suggesting the important role of environmental factors and genetic background. In some rare cases, with early onset, additional genetic defects are identified: PKD mutations in the second allele or other genes such as PKHD1o HNF1B. Mosaicism and the presence of hypomorphic alleles contribute to further increase the genetic complexity of this condition [245]

Prognosis is strictly linked to:

- Type of gene: PKD1 mutations are associated with major total kidney volumes (HtTKV) and minor GFR. They have a worse prognosis and lead to ESRD with a need for RRT at an average age of 58 years. Patients with PKD2 mutation require replacement treatment 10 years later.
- Type of mutation: truncating mutations are linked with less polycystine 1 residual activity.
- From other genetic and environmental factors within the same family phenotypes can show wide differences both in terms of progression towards ESRD and extra renal symptoms [246]. ADPKD is linked by the appearance and subsequent expansion of cortical and medullary renal cysts (100% of cases), which progressively lead to end-stage renal disease (ESRD) with a GFR decrease of 5 mL/min/year. Renal function can remain stable for several decades, despite the progressive increase in the number and size of cysts. This is due to compensatory glomerular hyperfiltration by normal glomeruli, which preserve renal function within the normal range. Only when most of the nephrons have been destroyed, renal function is reduced, usually after the fourth decade, until ESRD is reached. A wide variety of environmental factors have been studied for their impact on CKD progression in ADPKD patients: the better validated are high caffeine intake, high protein intake, low water intake and smoking [247,248].

Diagnosis is based on the following recently revised ultrasound criteria:

- Three or more unilateral or bilateral cysts for individuals aged 15–39 years
- At least two cysts in each kidney for individuals aged 40 to 59 years
- At least four cysts in each kidney for individuals aged >60 years [249].

A negative renal ultrasound beyond the age of 40 years excludes disease, between 20–40 years, a negative ultrasound should be followed by a CT or MRI scan. Criteria for the diagnosis using CT or MRI have recently been published with a total of >10 cysts being sufficient to define ADPKD [250].

The hepatic cysts arise from uncontrolled proliferation and dilation of the bile duct epithelium and also from alteration of the AMPc pathway. Hepatic polycystosis prevalence in ADPKD increases with age (in the CRISP cohort 58% between 15 and 24 years, 85% between 25 and 34 years, 94% between 35 and 46 years), risk factors for cysts increase are female sex, exogenous estrogens and delivery [251].

Commonly, hepatic involvement is silent, in relation to hepatomegaly it may appear as pain dyspnea, dyspepsia caused by organ volume. Complications given by the mass effect are also: obstruction of hepatic venous efflux, caval and/or portal compression

and obstructive jaundice. Other complications could be caused by cysts bleeding, infection or rupture. Laboratory tests can show gamma-gt and, more rarely, slight rises of alkaline phosphatase. Only rarely mass effect is very symptomatic with the need for LT [252].

Other extra-renal manifestation are frequent, such as hypertension (50%–70%), valvular defects (25%) and intracranial aneurysms (12%) [253].

6.2. Relevance of prognostic scores

Scores applied in ADPKD are able to predict an individual's risk of developing ESRD using a single total kidney volume (TKV) or genetics test linked with clinical information.

The Mayo classification requires demographic data such as patient age, height, and TKV. The TKV can be calculated employing a TKV calculator available online using a single representative coronal image. The calculator requires coronal and sagittal length and width and depth measurements of both kidneys to be entered using images obtained by CT without contrast or MRI without gadolinium and an expert radiologist [254].

An important caveat of the Mayo classification is that it does not apply to patients with atypical ADPKD, constituting 5% of patients, who have unilateral, asymmetrical, or segmental cyst burden. Such patients are at lower risk for progression because the spared kidney helps preserving the GFR.

The PROPKD score is a prognostic score that needs genetic testing (PKD1 vs. PKD2 mutation and truncating vs. non-truncating PKD1 mutation) connected with the following parameters: gender, presence of hypertension before 35 years of age, occurrence of the first urologic event before 35 years of age. The PROPKD score splits patients into low (0 to 3 points), intermediate (4 to 6 points) and high risk (7 to 9 points) of progression to ESRD, with corresponding median ages for ESRD onset of 70.6, 56.9, and 49 years.

PROPKD can be applied only if the genetic mutation is recognized after 35 years in asymptomatic patients [255,256].

6.3. Role of medical treatment

The pharmacological strategies tested in randomized controlled trials with positive clinical outcomes remain mainly aimed at reducing the volume of the liver and kidney cysts; treatment modalities include not just radiological and surgical procedures but also medical therapies which mechanism of action is mainly focused on reducing the levels of intracellular cAMP responsible for cyst formation: somatostatin analogues (octreotide, lanreotide), mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) and the vasopressin V2 receptor antagonist tolvaptan.

Tolvaptan

Between 2015 and 2018 both the European Drug Agency (EMA) and the Food and Drug Administration (FDA) approved tolvaptan (Jinarc), as an effective medication able to slow renal function declining in fast-progressor affected patients, based on the results of the clinical trial TEMPO 3: 4 and TEMPO 4: 4 [257–259].

TEMPO 3:4 (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) was a multicenter, randomized, placebo-controlled trial, in which the long-term safety and efficacy of tolvaptan (titrated between 60 mg / day and 120 mg / day) were compared with a placebo in 1445 adult patients with ADPKD from January 2007 to January 2012. The rationale of the therapy is based on the evidence that the AVP antagonists (Vaptani), by preventing the link with their receptor, cause the suppression of CAMP with a consequent increase in the excretion of free water (aquaporine) and reduction of the urinary osmolarity and renal cysts proliferation.

The inclusion criteria for the trial were: male or female patients aged between 18–50 years, with a certain diagnosis of ADPKD, CCr 60 mL/min, TKV > 750 (thus defined as rapid progressors). Tolvaptan reduced the rate of decline in kidney function from 5.5% to 2.8% at three years and the rate of clinically significant kidney pain. 8% of patients in the treatment group discontinued the trial drug because of an increased aquaresis (thirst, polyuria, nocturia, and polydipsia), and 4.9% of patients who received tolvaptan had elevations of alanine aminotransferase to greater than 2.5 times the upper limit of the normal range. Approximately 10.9% of patients in the tolvaptan group had adverse hepatic events compared to 5.3% in the placebo group. The most common manifestation was ALT elevation three times the upper limit of normal. Hepatocellular injury occurred between 3 and 18 months after starting tolvaptan, all cases showed resolution in LFTs after stopping the drug. In the REPRISE (Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD) multicenter, randomized trial including patients not enrolled in the TEMPO trial, showed that tolvaptan may slow the decline in kidney function, even if the baseline eGFR was significantly reduced. This was able to a multicenter, randomized trial that examined the effect of tolvaptan in patients with ADPKD aged 18 to 55 years with eGFRs of 25 to 65 mL/min/1.73 m2, and those aged 56 to 65 years with eGFRs 25 to 44 mL/min/1.73 m^2, with evidence of declining eGFR of at least 2 mL/min/1.73 m^2. REPRISE included an eight-week pre-randomization period, during which patients were sequentially administered a placebo and tolvaptan to assess their tolerance to tolvaptan. Patients who did not tolerate tolvaptan at a dose of 60 mg in the morning and 30 mg in the evening were not randomized, leaving a final sample size of 1370 patients. At 12 months, the change from baseline eGFR was lower among those assigned tolvaptan compared with the placebo (-2.34 vs. -3.61 mL/min/1.73 m^2); the group difference was 1.27 mL/min/1.73 m^2 (95% CI 0.86–1.68) [260].

While there is consensus among international recommendations that the drug should only be used in patients with a high risk of rapid progression, identification criteria for rapid progression vary: nowadays 6 assessment strategies are known worldwide, based on eGFR changes, kidney size and genetics.

Somatostatine analogues

Most data come from the 3 wide trials:

- the Developing Interventions to Halt Progression of ADPKD 1 (DIPAK 1) trial, in which 309 patients with PKD and eGFR between 30 and 60 mL/min/1.73 m^2 were randomly assigned to lanreotide, 120 mg subcutaneously once every four weeks for 2.5 years or with usual care. Although lanreotide reduced the TKV (4.1 vs. 5.6% per year), it failed to slow the loss of eGFR (mean difference between both groups was −0.08 mL/min/1.73 m^2 per year and was not significant) and did not prevent the development of ESRD (2 vs. 1%). The drug also led to more serious side effects, including hepatic cyst infection (5 vs. 0%), as well as diarrhea and abdominal pain [261].
- ALADIN 1 academic, multicentre, randomised, single-blind, placebo-controlled, parallel-group trial was conducted in five hospitals in Italy. Adult patients with estimated glomerular filtration rate (GFR) of 40 mL/min per 1•73 m^2 or higher were randomly assigned to 3 year treatment with two 20 mg intramuscular injections of octreotide-LAR (n = 40) or 0.9% sodium chloride solution (n = 39) every 28 days. The study conducted in 75 pts failed to slow eGFR decline between the two groups [262].

- ALADIN 2 study, a very similar study to the previous ALADIN 1 conducted as a parallel-group, double-blind, placebo-controlled phase III trial and based on the use of octreotide in patients with CKD stage 3b or 4 (GFR 15–40 mL/min); in the study it was observed that octreotide-LAR slowed cysts growth and delayed progression to ESRD. These patients (at high risk of kidney failure), given the cost of the drug, could be the only ones worth treating with this drug. However, the reduction of kidney cyst growth may potentially be of interest to avoid nephrectomy before KT in cases of very large kidneys [263].

mTOR-i

A proof-of-concept randomized, crossover study (SIRENA) suggested that rapamycin stabilized cyst growth at six months. Two randomized trials confirmed a slowing of cyst growth (statistically significant in the first year of treatment) but showed no benefit on renal function, with side effects including proteinuria, leukopenia, thrombocytopenia and hyperlipidemia, which resulted in a high rate of discontinuation (approximately 35%). An additional consideration is that there is still uncertainty on the dosage necessary to achieve biological efficacy [264–266]

6.4. What is the impact of radiological and surgical treatment on gastro-intestinal symptoms control?

The liver and kidney cysts increase with the aging and growth rate of polycystic liver was estimated at 0.9–1.6% in 6–12 months in different clinical studies [267,268].

An observational study from The Netherlands conducted from five tertiary liver centers collected clinical data on 188 PCLD indicated that more than 80% of patients were female and aged nearly 50 years. The great majority were symptomatic at the time of presentation and the presence of PRKCSH or SEC63 mutation and female gender are associated to more severe cases [269].

The most frequent symptoms in PLD are associated to massive abdominal distension by enlarged liver, with feeling of fullness, abdominal pain and discomfort, commonly dyspnea in supine position, early satiety and progressive reduction of food consumed with muscle mass reduction and sarcopenia. The other frequent symptoms are associated with cysts bleeding and infection.

The Gigot criteria classified polycystic liver disease in three stages according to the cysts spread, number and volume [270]; Gigot 1 is characterized by < 10 large (>10 cm) cysts, Gigot 2 by diffuse spread of medium-large cysts with large parenchymal areas conserved, Gigot 3 by a very large number of small-medium size cysts diffuse in all the parenchyma with very few liver areas preserved.

Radiological and surgical treatments of polycystic liver disease are indicated only in symptomatic patients [271,272] with impaired quality of life and includes TC or ultrasound- guided aspiration or sclerotherapy, transcatheter arterial embolization, fenestration or hepatic resection.

Aspiration/sclerotherapy

This is a minimally invasive treatment for large (>5 cm) symptomatic cysts including complete aspiration of cystic fluid followed by sclerosing liquid injection that can produce destruction of cystic epithelium, inhibiting fluid production.

A literature review published in 2000 [273] described 292 symptomatic patients treated with aspiration/sclerotherapy, cyst diameter ranged from 5 to 20 cm and in the majority the treatment was conducted in a single session.

The majority of patients had complete or partial symptoms resolution with 21% of cysts recurrence. Regarding safety, this technique is minimally invasive and the most frequent symptom is transient abdominal pain due to ethanol induced peritoneal irritation.

A recent study including 21 patients with PLD treated with aspiration followed by ethanol sclerotherapy showed that after 6 months there was a significant decrease not only of cyst volume but, more importantly, a significant decrease of symptoms measured by a PLD-Q score [274,275]. The study also showed also that responders had significantly larger cyst volumes compared to non-responders.

Transcatheter-arterial embolization

Because the cysts in PLD are mostly supplied from hepatic arteries but not from portal veins, transcatheter arterial embolization (TAE) of the hepatic artery branches that supply the major hepatic cysts might lead to reduction of the cyst and liver size.

So far only two small case series from Asian centers have been published, with a total liver volume decreased by 26–32% at 1 year and PLD-related severe symptoms remarkably improved in more than 80% of the treated patients [276,277].

Given the small experience with this approach, TAE should not be considered outside the setting of clinical trials.

Fenestration

This is a surgical technique involving cysts aspiration, incision and deroofing aiming to reduce the liver volume; it is indicated in Gigot type I and II when aspiration has failed. The technique can be minimally invasive if approached by laparoscopy.

A recent systematic review and metanalysis including 15 studies with a total of 146 PLD patients treated showed that fenestration was able to recover from abdominal symptoms in over 90% with symptomatic recurrence rate of 33.7% [278].

The 29% post-operative complications, with conversion from laparoscopic to open surgery, mostly for bleeding, was required in 8.2% and the procedure related mortality was 2.3%.

The most frequent complications were biliary leaks, ascites, infections and pleural effusions. The relatively high complication rate in PLD treated with fenestration may be related to an altered anatomy associated to a wide cysts spread in the liver and in some studies to a high number of cysts fenestrated during the procedure [279–281].

Also in the choice of this less invasive surgical technique, we have to consider potential complications such as abdominal adhesion, infections and biliary leaks, which can make the subsequent liver transplant technically difficult.

Hepatic resection

Segmental hepatic resection may be considered only in Gigot II stage and only in patients with massive hepatomegaly in whom a sufficient extent of normal liver can be maintained and without significant vascular or biliary system modifications.

The extension of resection depends on cysts position and, in order to avoid post-operative hepatic dysfunction, the residual liver volume should not be less than 26–30% with the remaining liver containing few cysts [282,283].

The vascular and biliary distortion caused by the cysts increase the principal causes of post-operative complications such as abdominal infection, biliary leaks and fistulas.

Not many centers have acquired an extensive experience in these technically difficult hepatectomies and data regarding efficacy and safety are scattered.

The collective data obtained from published studies including less 337 patients showed that this procedure is associated with

a high efficacy in resolving symptoms in 75%, but burdened by a significant morbidity (51%) and mortality (3%) [284].

Moreover, previous resection could be a potential source of abdominal complication and adhesion that might complicate any future liver transplantation; it is for this reason that resection is considered only when fenestration alone is not effective or for patients in whom a left lobectomy is sufficient to relieve symptoms. Any extensive or technically difficult hepatectomy should be carefully evaluated in potential candidates for LT [281,282].

A recent mono-centric study describing 11 patients with PLD treated with open approach extended resection and associated with marsupialization technique reported a very high success rate with resolution of symptoms in all patients without major complications, no need for reoperation, and no deaths [285].

In conclusion, hepatic resection in PLD should be performed only in tertiary centers with a wide experience in hepato-biliary surgery and also in LT.

6.5. Management of patients with polycystic disease in the transplant setting

Kidney transplant is a safe method of renal replacement therapy in patients with PKD, with low morbidity and high graft and patient survival rates, and it is common knowledge that KT from a living donor has a much better graft outcome than that from a deceased donor, in particular for pre-emptive KT [286,287].

Post-transplant morbidity appears not to be increased in ADPKD patients as compared to other, non-diabetic transplant recipients. New onset diabetes, gastrointestinal (GI) complications, erythrocytosis, urinary tract infections, thromboembolic complications, and haemorrhagic stroke are reported as more frequent complications after transplant [288,289].

It is well known from the literature that ADPKD kidney transplant recipients have a high risk of developing new onset diabetes after transplantation (NODAT), indeed Cheungpasitporn et al. published a meta-analysis including 12 cohort studies, comprising 1379 ADPKD patients out of a total number of 9849 patients who received a KT, finding a relative risk of post transplant diabetes mellitus higher in ADPKD than in the other KT patients [290].

Transplanted patients are more susceptible to infective complications due to the immunosuppressed status, so it should be no wonder if kidney and liver cyst infections, intestinal diverticulosis and heart valve disease occur after KT more frequently in ADPKD. However, in a survey on a relatively large group of KT patients, the incidence of the overall number of urinary tract infections, including pyelonephritis, was comparable between ADPKD KT and other groups of patients. Cyst infections in an immunosuppressed patient can rapidly evolve into a septic state and they are often a challenging diagnostic and therapeutic problem [291].

In the suspicion of an infective process, a fast and complete diagnostic protocol and specific antibiotic therapy should be started as soon as possible.

It has been suggested that 18F-fluorodeoxyglucose positron emission tomography–CT (18-FDG PET–CT) can improve sensitivity and specificity in the diagnosis of cyst infections in ADPKD as compared to CT and MRI [292].

6.5.1. Work up in transplant candidate with polycystic liver-kidney disease

Mono or bilateral nephrectomy in patients with ADPKD is indicated in cases of recurrent urinary tract infections and haematuria, neoplastic degeneration, compression syndrome and refractory pain. In candidates for KT, the most common indication is the need for space to avoid compression of the graft.

Enlarged native kidneys may cause compression to the transplanted kidney, contributing to complications during transplant surgery as well as vascular thrombosis and urine flow complications after KT. The ideal timing and approach (laparoscopic vs. open) of this type of surgery is not clear and it depends on the symptoms or policy of the center [255]. A laparoscopic approach should be evaluated for small-size native kidneys [293].

As for intracranial aneurysms (ICAs) detection, 2014 KDIGO recommend screening only in ADPKD patients with a family history of ICAs or subarachnoid hemorrhage and not as routine screening. Recently Sanchis et al. showed in a pre-symptomatic screening on 812 ADPKD patients that also patients without a family history of ICAs or subarachnoid hemorrhage, showed an increased prevalence of aneurysms compared to the general population [294].

Light MRI without gadolinium enhancement is the method of choice if screening is undertaken. Individuals with ICAs should be revaluated every 6–24 months. For patients with positive family history but without ICAs on screening should have exams performed every 5 to 10-years [295].

The CST transplant eligibility guidelines make no distinction between stroke and transient ischemic attack; a delay of at least 6 months is suggested for each condition. The retrospective study published by Nurmonen et al. that enrolled 4436 patients with ICAs, of whom 53 (1.2%) had ADPKD (95% CI 0.9%–1.6%, 45% male) showed that the cumulative risk of de novo ICAs formation was 1.3% per ADPKD patient-year and 0.2% in the general population, and ruptured IAs were significantly smaller than in the general population. Furthermore, in Cox analysis, the disease was an independent risk factor for de novo ICAs formation [296].

Some results were also reported in a Dutch meta-analysis of 53 cohorts and 369 patients with ADPKD with IA, 9–36% of ruptured ICAs were less than 5 mm and occurred not only often in a familial setting of subarachnoid hemorrhage, but also at an earlier age and more often in men [297]. Each transplant center should decide the criteria for the screening and type of surgery in an ADPKD patient on the KT waiting-list, according to local expertise [298].

It is well known from the literature that ADPKD kidney transplant recipients have a high risk of developing NODAT, Caillard et al. suggested in an article published in 2011 that the Oral Glucose Tolerance Test (OGTT) may be considered the gold standard for demonstration of pre-transplant glucose metabolic status and prediction of NODAT, despite the cost, inconvenience and potential for day-to-day variability of this test [299].

The presence of cystic lesions in a potential living kidney donor requires careful disease exclusion for ADPKD and other genetic disorders. Multiple renal cysts may indicate polycystic kidney disease, although 11% of individuals over the age of 50 will have one or more simple renal cyst. In such a situation, a detailed family history, abdominal MRI and sometimes a genetic test are required. Pei et al. defined specific ultrasound criteria related to family history and age of the patient to diagnose ADPKD. In those under 40 years with a positive family history, the presence of two or more cysts (unilateral or bilateral) indicates ADPKD, but it should be underlined that a negative scan at this age is associated with a 4% false negative rate. In many borderline cases, in particular in young subjects, the sensitivity of US is relatively limited, so it is recommended to perform abdominal TC or MRI [250].

Instead for those aged 40 to 59 years, the absence of at least two cysts in each kidney gives a 100% negative predictive value for ADPKD, whilst for those older up to four cysts are acceptable in each kidney. It is important to consider that in 10% polycystic disease can arise from spontaneous mutations with a negative family history. Genetic testing may permit more accurate disease exclusion for donors when combined with radiological screening. Indeed, many units would not use a kidney from a relative under 30 years of a patient with ADPKD who had even just one renal cyst without mutation screening [300].

6.6. Liver and kidney transplantation in the treatment of Caroli syndrome

Two different phenotypes of Caroli's disease (CD) can be recognized; type I characterized by a pure biliary cystic dilatation and type II in which cystic dilatation is associated with congenital hepatic fibrosis (CHF) and/or autosomal recessive kidney polycystic disease (ARPKD). CD can occur at any age, in general patients younger than 40 more frequently carry type II CD whereas older patients carry Caroli type.

The common etiology of these fibrocystic diseases is related to ductal plate malformation involving large bile ducts for CD and small ducts for CHF.

The renal involvement, associated with up to 60% of CD, implies a dilation of the collecting renal tubules; the association between CHF and ARPKD is caused by mutations in PKHD1 that encode fibrocystin and polyductin, which are proteins localized in the primary cilia. This mutation leads in two distinct phenotypes; the first, which concerns pediatric patients with predominantly renal involvement and the second, emerging at more advanced age in pediatric patients and young adults with a primary hepatic involvement.

The liver involvement can be segmental or diffuse and the degree of fibrosis and intrahepatic bile duct dilation is highly variable. In a recent published series from Asia 30 patients with CD were described; nine were diagnosed with type I CD, including three who also had chronic cholangitis, and 21 were diagnosed with type II CD, including 14 with cirrhosis and two with secondary biliary cirrhosis [301].

The majority of patients were symptomatic, the more frequent signs were abdominal pain, fever, jaundice related to cholangitis and variceal bleeding, thrombocytopenia and anemia in patients with associated CHF.

The prognosis of patients with CD is poor, especially in those with diffuse cystic involvement and associated with CHF; a review of 50 patients published in 1995 revealed that mortality was 46% at a mean time from diagnosis of 9 months, death was primarily caused by sepsis, liver abscess and liver failure [302].

Caroli's disease or syndrome is a rare indication for liver alone or combined liver-kidney transplantation; LT is indicated only in symptomatic patients and in diffuse bile ducts dilatation involving both liver lobes and when associated with congenital hepatic fibrosis and PH.

Localized cystic involvement in the absence of portal hypertension can be treated with segmental hepatectomy; in the presence of biliary stones in extrahepatic ducts endoscopic procedures could be the first options.

In patients with diffuse involvement and with associated portal hypertension, LT could be considered at the first appearance of the symptoms because recurrent cholangitis can lead to a complicated transplant procedure and post-operative course due to an increased infection risk; mortality after LT was higher in patients with CD with cholangitis at the time of LT [303].

The retrospective analysis from Pittsburg transplant center described the clinical outcome of 33 patients with CD transplanted between 1982 and 2002; short-term graft and patient survival at 1 month was 83% and 86%, whereas overall long-term graft survival rates at 1, 5, and 10 years were 73%, 62%, and 53%. Sepsis was the most frequent cause of death, in particular in patients who experienced cholangitis pre-LT [304].

Previous bilio-enteric surgery should be considered with caution in a potential candidate for LT considering the increased risk of cholangitis due to intestinal reflux in the biliary system in Roux-en-Y hepaticojejunostomy. In conclusion, prevention and early treatment of cholangitis episodes are strongly recommended and the patients should be referred to LT at the first cholangitis episode.

6.6.1. Combined liver-kidney transplantation in Caroli's Disease

Data regarding kidney and LT in this population are scarce.

The revision of the European Liver Transplant Registry showed an overall survival of 80.9% in 110 patients transplanted with CD during the period 1968–2003, sixteen (14.5%) patients had SLKT [305].

Overall experience in the US showed that of 104 CD recipients transplanted between 1987 and 2006, 96 underwent liver alone and 8 combined liver-kidney transplantation, with patient and graft survival comparable to or better than that of patients transplanted for other causes [306].

A French experience published recently regarded 14 ARPKD aged 3–25 who underwent KT; three patients had an orthotopic LT, performed 7–20 years after the KT in two cases and simultaneously to KT in one case. Mortality for the isolated KT group was 2/14 and 1/3 in combined liver -kidney transplant. In all cases, mortality was due to sepsis episodes caused by cholangitis [307].

In another recent study of 45 young adult ARPKD, the mean age was 21 $\pm$ 3, renal function was CKD stages 1 to 3 in more than 50%, 41% of patients received renal replacement therapy.

Liver disease appeared later, with splenomegaly documented in 57% and recurrent cholangitis in 10% of patients; six patients received CLKT or LT during childhood and adolescence [308].

ARPKD mainly affects childhood, with symptoms appearing in most cases in the perinatal or pre-natal period, but a substantial number of children with early diagnosis reach end-stage renal disease in adulthood and others are not diagnosed until they are young adults.

6.7. Indications for isolated liver or combined liver-kidney transplantation in polycystic diseases

ADPKD affects up to 0.2% of the general population [309], whereas isolated PLD has a prevalence of less than 0.01% [310]. Both ADPKD and PLD are autosomal dominant and 75%–90% of patients with ADPKD have associated PLD [311].

Abdominal or back pain, dyspnea and gastro-intestinal symptoms such as nausea early satiety and malnutrition are principally related to liver or combined liver/kidney volume with a more relevant role for liver than kidney [312].

In a large recently described cohort of 309 ADPKD patients abdominal pain was reported by 27.5%, whereas 61% of the patients experienced GI symptoms [309].

Females are overrepresented among patients with GI symptoms [268,313] while it is not clearly established if the higher GI symptoms prevalence in females is caused by differences related to gender or to different liver size in the two genders.

Females have larger height/total liver volume (hTLV) compared to males, and when adjusted for hTLV, variations in symptom severity between males and females disappeared [309].

In contrast to polycystic kidney disease, PLD is not associated with organ failure and symptoms such as dyspnea, early satiety, malnutrition and severe sarcopenia are prevalently related to abdominal compression, the patient can develop intractable pain affecting their days and inability to sleep due to the enlarged liver; when PKD is associated with Caroli's syndrome symptoms are usually characterized by a portal hypertension complication of recurrent cholangitis [314,315].

The first report on LT in a patient with polycystic liver-kidney disease was by Kwok and Lewin in 1988, since then liver or combined liver-kidney transplantation has remained a rare indication, therefore the appropriate timing and sequence of both organs transplanted can be difficult.

Guidelines published in 2006 have clarified PLD patient selection for LT [316]:

- Satisfy criteria for massive PLD (total cyst: parenchyma ratio >1) and have a complication of PLD that is likely to resolve after LT.
- Are not candidates for, or have failed non-transplant interventions; malnutrition may be considered a primary contraindication to non-transplant surgery.
- Symptoms that can be attributed to massive PLD, such as cachexia, ascites, portal hypertension (variceal bleeding), hepatic venous outflow obstruction, biliary obstruction, cholestasis, or recurrent cyst infection.
- Severe malnutrition (assessment made on the basis of hypoalbuminemia or decreased lean body mass).
- Serum albumin <2.2 mg/dL.

In many cases abdominal expansion symptoms can anticipate the end stage of kidney failure therefore the indication for KT, such as in other combined transplants, can be frequently established in a pre-dialytic phase. Concerning the liver disease these patients do not suffer from a life-threatening condition even if their quality of life is dramatically reduced and sarcopenia and malnutrition could be a contraindication to transplant due to overly severe malnutrition and frailty.

The US experience from UNOS database analyzed 107 adults with ADPKD who underwent combined liver/kidney or an isolated liver transplant for PLD/PKD showed that only 58% were on dialysis prior to transplant; moreover patients with combined liver–kidney transplant had better survival than those with liver transplant alone, showing survival rates of 91% vs. 87% at 1 year, 90% vs. 82% at 3 years and 90% vs. 77% at 5 years. The authors speculated that candidates for liver transplant alone had poorer nutritional status and severe muscle wasting, and more frequently complications related to infection and portal hypertension than candidates for combined liver-kidney [317].

In patients who undergo an isolated liver transplant we should consider that the immunosuppressive therapy with CNI could worsen the residual kidney function, usually one year after LT a mean reduction in GFR of 40% can occur; therefore, residual kidney function should be accurately evaluated before choosing between isolated or combined transplant. Moreover, the increased risk of sepsis after transplant due to bacterial reservoirs in the remaining polycystic kidneys should carefully considered in the case of liver transplant alone.

In general, a GRF > 30 mL/min/1.73 m suggests a solitary LT even if in a case-series published in 2006 all patients with a GFR < 60 mL/min underwent a KT in the following 4 years [318].

6.7.1. Conditions in which a delayed strategy could be preferred to a simultaneous one in combining liver-kidney transplantation

With the adoption of MELD score as algorithm for liver allocation, the highest priority shifted to patients with renal insufficiency and a rapid increase of SLKTs performed yearly occurred in many transplant centers around the world [319].

Although the first experiences demonstrated no adverse impact of the MELD allocation system on outcomes of SLKT, following studies reported a declining of survival in SLKT in the MELD era; moreover, other studies revealed that delayed graft function (DGF) of the renal allograft was found to be the strongest predictor of diminished survival [319].

UNOS data published in 2008 showed that in SLKT patient survival had declined from 2002 in comparison to a continuous increase in LT alone. The main raison for this decline of survival in combined LKT in recent years seems to be related to a worse clinical condition of candidates who are older, more often hospitalized, and more often with HRS. In addition, the lower survival observed after SLKT in the MELD era occurred despite the higher quality of liver and kidney grafts allocated to these recipients [231].

Historically, combined liver-kidney transplant was performed in a single procedure with KT following LT; the complexity of SLKT derives not only from the intra-operative technical difficulty, but also from the recipient's pre-operative clinical conditions and from intra- and post-operative management.

Liver recipients can in many cases be coagulopathic and hemodynamically unstable, needing vasopressors from the transplant beginning; moreover, in order to avoid hepatic congestion and to optimize graft recovery low central venous pressure should be maintained during the operation and in the post-operative period. In these hemodynamic conditions, in particular when high doses of vasopressor are required, kidney allograft performs poorly and in addition kidney function could be compromised by a severe phase of reperfusion injury favoring ATN.

The consensus guidelines have not established criteria to identify recipients at risk of grafted kidney failure but recent experiences showed a 20% short-term loss of transplanted kidneys after SLKT, strongly suggesting that renal transplantation should be deferred in liver recipients at high risk for renal allograft futility defined as patient death or need for RRT at 3 months. The authors identified as high risk for renal allograft futility (RAF) those recipients with greater laboratory MELD, lengths of pre-transplant hospitalization, and those who received donor organs with higher liver donor risk index (DRI) and kidney DRI and had longer kidney cold ischemia time. Intra-operatively, recipients with RAF were more likely to require damage control during LT [320].

Recently a novel management approach was performed in order to optimize the physiological environment for KT, placing the kidney graft on a hypothermic pulsatile perfusion machine and delaying the transplant for 2 to 3 days post-LT after hemodynamic stabilization and control of coagulopathy finally permitted a complete vasopressor weaning. This first experience showed that delayed graft function was significantly lower in "delayed strategy" with a higher eGFR during the 4-year follow-up period; moreover the delayed technique was safe without any deleterious effects related to hypothermic perfusion.

Patients with polycystic disease, due to the technical difficulty of the hepatectomy, are at higher risk of longer intra-operative time, bleeding and hemodynamic instability at the end of liver transplant: in these conditions, a delayed strategy could be suggested.

Recently the delayed strategy was applied on two patients with ADPKD, this approach permitted KT to be performed in a condition of hemodynamic stability and complete weaning from vasopressor; both patients are alive at 5 months after transplantation with complete recovery of liver and kidney graft function [321]. For KT, placing the kidney graft on a hypothermic pulsatile perfusion machine and delaying the transplant for 2 to 3 days post-LT after hemodynamic stabilization and control of coagulopathy finally permitted a complete vasopressor weaning. This first experience showed that delayed graft function was significantly lower in "delayed strategy" with a higher eGFR during the 4-year follow-up period; moreover, the delayed technique was safe without any deleterious effects related to hypothermic perfusion.

Patients with polycystic disease, due to the technical difficulty of the hepatectomy, are at higher risk of longer intra-operative time, bleeding and hemodynamic instability at the end of LT: in these conditions, a delayed strategy could be suggested.

6.7.2. Immunosuppression issues be addressed in liver-kidney polycystic diseases

In the context of combined liver-kidney transplantation, previous experimental models and clinical experience have suggested that the liver may confer immunological protection through the

capacity to absorb and remove donor-specific antibodies, reducing or preventing humoral rejection of another graft from the same donor [322,323].

This concept has been reviewed after recent reports of antibody-mediated rejection (AMR) in CLK from the same donor with preexisting DSA [324–326].

From a 2011 analysis of the Scientific Registry of Transplant Recipients data about 2484 CLK, 12% had a positive cross match, seeming to confirm that pre-sensitization confers a higher risk of graft loss and patient mortality even in patients submitted to combined liver-kidney transplant [327], overturning the concept of liver-immunological protection.

Regarding immunosuppression in combined liver-kidney transplant in polycystic disease, the guidelines don't recommend a specific immunosuppression regimen; in general permanence of native kidney with potential infected cysts or a transplant procedure at a very late stage of physical exhaustion and malnutrition may cause higher susceptibility to infection in patients with polycystic liver or kidney disease [328–330], therefore in this setting any condition of over immunosuppression should be avoided.

Questions

Q36. What is the genetic background, phenotypic expression and natural history in polycystic kidney and liver disease?

ADPKD occurs in 1 out of every 500 to 1000 live births and is the most common cause of inherited renal failure The disease is a consequence of mutations in PKD1 or PKD2, encoding polycystin 1 (PC-1) and polycystin 2 (PC-2), respectively. 85% of patients with PKD1 mutations typically display a more severe disease course, especially when they have truncating mutations, with ESRD occurring 20 years earlier than in the 15% of patients with PKD2 mutations (A).

ADPKD is characterized by the progressive development and growth of numerous bilateral renal cysts, resulting in urine concentration defects, hypertension, acute and chronic pain, kidney stones, haematuria, cyst and urinary tract infections, and, most importantly, renal function loss. A negative renal ultrasound beyond the age of 40 years excludes disease, a negative ultrasound before 40 years should be followed by a CT or MRI scan (1A).

Comment

ADPKD is the most common inherited renal disorder worldwide; two genes have been identified which encode two proteins (polycystin-1 and polycystin-2) that constitute the transient receptor potential polycystin subfamily of transient receptor potential channels. The disease is characterized by renal cysts and progressive renal failure due to progressive enlargement of cysts and renal fibrosis. An estimated 45% to 70% of patients with ADPKD progress to end-stage renal disease by the age of 65. Several studies underline that genetic testing is not needed, if not in a small percentage of patients; a firm positive diagnosis can be made by imaging together with the patient's parents or by the presence of extrarenal manifestations.

Q37. Which are the most reliable predictors of a rapid progression of kidney disease?I

Solid evidence available in the literature allow to identify TKV > 750 cc, PKD1 mutations (in particular if truncating), early hypertension, early and multiple macrohematuria episodes, RBF or GFR decrease at a young age as the most reliable predictors of a rapid progression of kidney disease (2A).

The Mayo Clinic group has recently proposed the Mayo imaging classification system, a score which categorizes patients into five prognostic classes based on a correlation between TKV height adjusted obtained with MRI or CT images and patient age. Classes 1C, 1D, and 1E are defined as high risk for progression to end-stage renal disease. PROPKD instead identifies three classes of risk through a correlation genotype-phenotype. Rapid progressors are defined as patients who achieved the score 7–9 (1A).

Comment

TKV > 750cc, PKD1 mutations (in particular if truncating), early hypertension, early and multiple macrohematuria episodes, RBF or GFR decrease at a young age are the most reliable predictors of a rapid progression of kidney disease. The Mayo prediction classification appears to be a more sensitive measure of disease progression as in the early stages of disease there is little change in renal function but detectable changes in TKV. In addition to this, the PROPKD scoring system cannot be applied to patients younger than 35 years and/or those missing clinical data.

Q38. What is the role of medical treatment (somatostatin analogue, mTOR inhibitors tolvaptan) in polycystic diseases progression?

Somatostatin, long-acting somatostatin (octreotide), and a somatostatin analog (lanreotide) may reduce kidney and liver cyst fluid accumulation among patients with PKD. However, these agents have not been shown to slow the progression of kidney function decline and have not negligible adverse events (1A).

The mammalian target of rapamycin (mTOR) signaling pathway may modulate disease progression in ADPKD, although there is an absence of evidence in clinical trials to recommend these for routine clinical use (1A).

Treatment with tolvaptan should be considered for patients who are classified as 1C and are younger than 50 years or have other risk factors for rapid progression (2B).

Comment

We suggest that all patients be referred to a multidisciplinary team for initial assessment and to determine what treatment should be initiated.

Q39. What is the impact of radiological and surgical treatment on gastro-intestinal symptoms control?

Radiological and surgical treatments of polycystic liver disease are indicated only in symptomatic patients with impaired quality of life and include TC or ultrasound-guided aspiration or sclerotherapy, transcatheter arterial embolization, fenestration or hepatic resection (2C).

Percutaneous aspiration followed by ethanol sclerotherapy lead to a significant decrease of symptoms and responders had significantly larger cyst volumes compared to non-responders (2C).

Transcatheter arterial embolization was applied only in small case series with a decrease of liver volume and significant reduction of symptoms (2D).

Surgical fenestration can relieve abdominal symptoms but post-operative complications and conversions from laparoscopic to open surgery are frequent (2D).

Also in hepatic resection technical complications are common and potentially risky in candidates for LT (2D).

Comment

The published clinical series pointed out high complication rates in the radiological and surgical treatment of symptomatic polycystic patients; therefore the different treatment options should be evaluated by a multi-specialty team in high-volume surgical and transplant programs in order to avoid complications that could compromise a future transplant decision

Q40. How to manage the transplant setting in patients with polycystic disease?

Kidney transplant is a safe method of RRT in patients with ADPKD. Post-transplant morbidity appears not to be increased in ADPKD patients as compared to other, non-diabetic transplant recipients, even if new onset diabetes, gastrointestinal (GI) complications, erythrocytosis, urinary tract and cysts infections, thromboembolic complications, and haemorrhagic stroke are reported as more frequent complications after transplant (Ungraded).

Comment

Kidney transplant is a safe method of RRT in ADPKD patients, with low morbidity and high graft and patient survival rates.

Data available in the setting of transplants in ADPKD derived from retrospective series; more data are required to establish how it will be possible to avoid these complications.

Q41. What is the most appropriate work-up in a transplant candidate with polycystic liver-kidney disease?

We recommend for all ADPKD patients with CKD G4-G5 (GFR $<$ 30 mL/min/1.73 m^2) who are expected to reach ESKD kidney transplant as the best option of renal replacement, with low morbidity and high graft and patient survival rates (1A).

It is common knowledge that the KT from a living donor has better graft outcome than from a deceased donor (1A).

Potential KT candidates should be referred for evaluation at least 6 to 12 months before starting dialysis to allowed identification/work-up of living donors and plan if pre-emptive transplantation is possible (Ungraded).

The presence of cystic lesions in a potential living kidney donor requires careful disease exclusion for ADPKD and other genetic disorders. In such a situation, a detailed family history, abdominal MRI and genetic test are required, in particular for potential donors aged less than 40 (Not Graded).

We recommend unilateral or bilateral nephrectomy before transplantation in ADPKD symptomatic patients (cysts bleeding, recurrent upper urinary tract infections, stones) (1C).

We suggest unilateral nephrectomy of asymptomatic ADPKD patients when there is a lack of space for the graft (2C). We do not recommend nephrectomy as a routine surgery in asymptomatic patients (Ungraded)

Screening for ICAs or subarachnoid hemorrhage is recommended only in ADPKD patients with a positive family history and not as routine screening (2D).

Light MRI without gadolinium enhancement is the method of choice if screening is recommended. ICAs should be revaluated every 6–24 months. For patients with positive family history but without ICAs on screening should have exams performed every 5 to 10 years (2C).

A high frequency of developing ICAs has been demonstrated, with an increased risk of rupture in ADPKD patient according to a Dutch meta-analysis, for this reason we suggest the screening of all ADPKD patients for ICAs, even those with a negative family history (Ungraded)

Each transplant center should establish the criteria for the screening, type of surgery in the ADPKD patient on the waiting list, according to the local expertise [298].

Comment

The published meta-analysis demonstrates the high risk of ICAs rupture in polycystic patients; therefore, the different screening approach should be evaluated by a multi-specialty team in high-volume surgical and transplant programs, in order to avoid complications that could compromise a future transplant.

Data available in the setting of transplant and living donation suggest the increasing role of genetics in the screening of potential donors.

Q42. What is the phenotypic classification of Caroli's disease?

CD is differentiated in two different phenotypes; type I characterized by a pure biliary cystic dilatation and type II associated with congenital hepatic fibrosis (CHF) ad/or autosomal recessive kidney polycystic disease (ARPKD) (2B).

Comment: Only systematic reviews concerning this rare condition have been published; two different phenotypes were identified.

Q42bis. What is the prognosis of Caroli's disease?

Prognosis is sharply different between CD type I and II; in type I the majority of patients are asymptomatic, and they can develop cholangitis only in a few cases, whereas in type II the prognosis is frequently poor due to the concomitant portal hypertension and kidney involvement, with a high short-term mortality (B).

Q43. How should the place of liver and kidney transplantation be assessed in the treatment of Caroli's syndrome?

Surgical treatment of Caroli's disease or syndrome is indicated only in symptomatic patients and in diffuse bile ducts dilatation involving both liver lobes and when associated with congenital hepatic fibrosis and portal hypertension (Ungraded).

Early treatment of cholangitis episodes is strongly recommended and patients should be referred for LT at the first episode of cholangitis (Ungraded).

Comment

Data available in the setting of transplants in CD derived from small retrospective series; more data are required to establish the indication and timing for transplantation in these patients

Q44. What are the indications and timing for mono or bilateral nephrectomy in liver-kidney transplantation?

Mono- bilateral nephrectomy in ADPKD patients is recommended before transplantation in the case of recurrent upper urinary tract and cysts infections, neoplastic degeneration, and compression syndrome, with refractory pain. Monolateral nephrectomy in asymptomatic patients is suggested in the case of lack of space for kidney transplant in the abdominal cavity. Native nephrectomy should not be done routinely due to the surgery complications and risk (2B).

Comment

The current recommendations derive from case series and mono-centric experiences. High risk of post-operative complications burdens surgery in patients with polycystic kidney disease.

Q45. What are the indications for isolated liver or combined liver-kidney transplantation in polycystic diseases?

Selection and evaluation for transplant should be suggested at the appearance of the first symptoms related to abdominal volume expansion or recurrent cysts infections; the choice between isolated liver vs. combined liver/kidney requires an accurate evaluation of residual kidney function and exclusion of potential bacterial reservoirs in the native kidneys (2B).

Comment:

An accurate evaluation of residual kidney function is the primary concern in the choice between isolated or combined liver-kidney transplants in polycystic disease. An average reduction of 40% in kidney function after LT should be considered

Q46. In combining liver-kidney transplantation what are the conditions in which the delayed strategy could be preferred to the simultaneous one?

Delayed strategy could be preferred in very sick recipients or with a huge liver or at high risk of longer intra-operative time, higher blood loss and need of vasopressor during the operation (Ungraded).

Comment

SLKT patient survival has declined in comparison to a continuous increase in liver transplant alone. The reason seems to be related to a worse clinical condition of candidates. Complicated technical procedure and hemodynamic instability of the recipient frequently characterize the intra-operative course of liver transplant in polycystic disease.

Q47. Should specific immunosuppression issues be addressed in liver-kidney polycystic diseases?

No specific immunosuppression regimen is recommended in transplant recipients for polycystic disease (2D).

Comment

Permanence of native kidney and malnutrition may cause high susceptibility to infection in patients with polycystic disease, therefore any condition of over-immunosuppression should be avoided.

Declaration of Competing Interest

Maria Cristina Morelli: has served on advisory boards for Abbvie, Gilead sciences, Shionogi srl.

Carlo Alessandria: reports personal fees from Alfasigma, outside the submitted work.

Sherrie Bhoori: has served as speaker bureau for Boston Scientific, Eisai, Ipsen, Kedrion.

Salvatore Petta: has served as Advisor and/or Speaker for AbbVie, Gilead, Intercept and Pfyze.r

Patrizia Burra: has served as Advisor and/or Speaker for Kedrion, Biotest and Chiesi Farmaceutici.

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