Abnormalities of renal function in chronic liver diseases

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Chişinău • 2016

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This guideline was approved by the Internal Medicine methodological profile commission from Department of Internal Medicine Nicolae Testemitanu SMPhU (Protocol N 1 from 02. 11. 2015) and Central Scientific methodical council of Nicolae Testemitanu SMPhU (Protocol N1 from 11.01.2016).

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Descrierea CIP a camerei naţionale a cărţii

Contents

List of abbreviations

AASLD	American Association for the Study of the Liver
ADH	Antidiuretic hormone
ALT	Alanine aminotransferase
AST	Aspartat aminotransferase
ATN	Acute tubular necrosis
AIN	Acute interstitial nephrites
AKI	Acute kidney injury
ARF	Acute renal failure
BUN	Blood urea nitrogen
C	Compliment
CT	Computer tomography
CCT	Clinical controlled study;
DNA	Deoxyribonucleic acid
GFR	Glomerular filtration rate
GN	Glomerulonephrites
HBsAg	Hepatitis B surface antigen
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B e antigen.
HRS	Hepatorenal syndrome
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HBsAg	Hepatitis B surface antigen
FSGS	Focal segmental glomerulosclerosis
IgA	Immunoglobulin A
IGAN	Immunoglobulin A nephropathy
IAC	International ascites club
IL	Interleukin
ITF	Interferon
KDOQI	Kidney disease outcome quality initiative
LC	Liver cirrhosis

LAM	Lamivudine
MELD	Model of end-stage liver disease
MN	Membranous nephropathy
MPGN	Membranoproliferative glomerulonephritis
MCGN	Mesangiocapillary glomerulonephritis
NAG	N-acetyl-beta-D-glucosaminidase
NE	Norepinephrine
NO	Nitric oxide
NSAID	Nonsteroidal anti-inflammatory drugs
LT	Liver transplantation
PG	Prostaglandin
PGE_2	Prostaglandin e2
PI	Pulsatility index
PDGF	Platelet-derived growth factor
PO	Plasma osmolarity
RAAS	Renin-angiotensin-aldosterone-system
RNA	Ribonucleic acid
RBC	Renal blood flow
UO	Urinary osmolarity
USG	Ultrasonography
SBP	Spontaneous bacterial peritonitis
SEC	Sinusoidal endothelial cells
SNS	Sympathetic nervous system
TIN	Tubulointerstitial nephritis
TNF	Tumor necrosis factor
TGF-β	Transforming growth factor-β

Introduction

Chronic liver diseases have frequent extra-hepatic manifestations, including kidney diseases. A lot ofadjacent glomerular diseases can be caused by viral infections based on the diagnostic criteria, including clinical and laboratory data.

It is not easy to establish the pathogenic links between aviral infection and renal disease. Often, one has to recognize the clinical syndrome, to integrate the serological finding, identify specific antigens related to the infective organism and demonstrate the presence of its antigenandantibodies in glomerular or tubular structures.In contrast to acute bacterial infection, chronic viral infection is characterized by higher concentrations of tissue viral antigens and they are accompanied by specific antibodies.

Many forms of infection may be complicatedbyglomerular diseases or interstitial nephritis, although only a minority of patients will be involved in treatment modalities. Some patients will develop chronic kidney disease, especially when persistent infection occurs.The most frequent and long-recognized virus-related glomerulopathies are those associated with HBV and cryoglobulinemia-related mesangiocapillary glomerulonephritis related to HCV infection.

Current knowledge of the management of patients with liver diseases and renal implications offers effective and safe options for antiviral treatment.Individualization and determination of less nephrotoxic and appropriate duration of antiviral treatment will enhance the prognosis of the disease.The interrelation of liver disease and kidney involvement hasevokedinterest over the years. In 1969 Ritz et al. detected the decrease in renal function in 13 (42%) from 31 patients with acute liver failure. Wilkinson S. et al. observed impaired renal function in 53% among 160 patients with cirrhosis. Epstein et al. performed renal angiography in patients with HRS and indicated the absence of blood flow in renal cortex.

Koppel et al. demonstrated the functionality and reversibility of hepatorenal syndrom in 1969 after cadaveric kidney transplantation from patients with liver cirrhosis to patients with end-stage renal failure.

It is allways interesting to identify in which liver and renal dysfunction coexist; diseases simultaneously involving the liver and the kidney, or presense of a primary hepatic disorder with secondary renal dysfunction, or vice versa.

Chapter I. Chronic virus hepatitis B related glomerulonephritis

Relationship between kidney and chronic hepatitis B

Following the discovery in 1965 of the Australian antigen renamed the hepatitis B surface antigen (HBsAg), Combes and col. first described the incidence of membranous nephropathy (MN) due to glomerular deposition of Australian antigen-containing immune complexes in a53-year-old man in 1971. Glomerular diseases can be caused by viral infections based on the diagnostic criteria, including clinical and laboratory data, molecular analysis of tissue. One of the most common human pathogens-the hepatitis B virus (HBV) is estimated to have infected about 350 million people worldwide. Extrahepatic manifestations of HBV infection can be present as glomerulonephritis, vasculitis or reactive arthritis.

Renal complications is among its most common extra hepatic manifestations and it is frequently manifested in the form of immune complex mediated glomerulopathy.Glomerular disease is more common in children than in adults, and in men than in women.The importance of HBV in clinical nephrology increases markedly in areas with endemic infection where the proportion of chronic HBV carriers can exceed 10% in the general population. In endemic areas, HBV is associated with both membranous nephropathy and mesangiocapillary glomerulonephritis, Renal biopsy with appropriate serological and molecular testing helps to define virus-related glomerular lesions and provides a prognostic and therapeutic guide. Antiviral agents remain the mainstay of the treatment.

Renal histopathologies include:immunoglobulin A (IgA) nephropathy. membranousglomerulonephritis (MN), mesangioproliferative glomerulonephritis and membranoproliferative glomerulonephritis (MPGN). Occurrence of focal and segmental glomerular sclerosis withHBV infection is rare. Khaira A, Upadhyay BK, Sharma A et al report two cases of hepatitis B associated FSGS. In both the cases, the presence of HBsAg was demonstrated by renal biopsy and both the cases showed response to treatment with lamivudine, thus indicating a possibleassociation between the viral infection and occurrence of focal segmental glomerulosclerosis(FSGS).

Chronic HBV infection is an etiological factor in the incidence of secondary glomerular disfunction and has a complex relationship with the evolution and the prognosis of the patients disease.HBV is not directly cytopathic to hepatocytes. The host immune response to virus-specific cytotoxic T lymphocytes it is specific for hepatocellular damage as well as viral clearance. Neonatal exposure to HBV when the immune system is immature results in minimal acute hepatitis, but this is fol-

lowed by chronic infection in 90% of subjects. After entering hepatocytes by endocytosis, the partially double-stranded viral genomic DNA is transported into the nucleus, where it is converted to circular DNA, which serves for transcription of viral mRNAs, which in turn are used for viral replication through reverse transcription and the production of viral DNA polymerase and other viral proteins. From a recent series that included 390 patients with membranous nephropathy showed that HBV was the underlying cause in 12% of patients.

Pathogenic mechanisms of hepatic glomerular disfunction

Both viral and host factors are involved in pathogenesisof glomerular disfunction.The genetic predisposition was reported. The main pathogenic mechanism in HBV-related glomerular diseases is the deposition of immune complexes in the glomerulus. The immune complexes are comprised of viral antigens and the antibodies. Inpatients with HBV-related glomerulonephritis various HBV antigens including hepatitis B surface antigen (HBsAg), hepatitis B early antigen (HBeAg), and hepatitis B core antigen (HBcAg) have been demonstrated. Immune deposition occurs predominantly in the subepithelial region andcan also involve the mesangial and subendothelial areas, depending on the size of the antigens and immune complexes. Possibly the low molecular weight of HBeAg might account for its ability to traverse the glomerular basement membrane and form the subepithelial immune deposits. Association between remission of proteinuria and clearance of HBeAg also provides indirect evidence that the antigen is involved in pathogenesis. The immune complexes then activate complements and glomerular injury contribute to the formation of membrane attack complex by the induction of proteases, oxidation injuryand acute phase response agents. Some authors have revealed upregulation of complement and coagulation pathways andreduced circulating C3 levels in mice that expressed HBsAg and HBcAg in the cytoplasm of renal tubular epithelial cells but without replication of the whole virus.

Moreover,circulating HBV DNA, and HBV holder also showed a higher circulating level of transforming growth factor-beta, a growth factor implicated in the potentiation of apoptosis and renal fibrosis.

Pathomorphological features of hepatic nephropathis

Different histological types of glomerular lesions have since been described in association with HBV infection, however, the most common is still MN. Glomerular capillary depositions of HBsAg, HBcAg and HBeAg in HBV-related MN nephropathy have been observed by various investigators. Hirose *et al.* had used F fragments of anti-HBsAg monoclonal antibody to demonstrate that capillary deposits were HBeAg . Using the same F fragment of anti-HBeAg monoclonal antibody and another monoclonal antibody against HBeAg, Lai *et al.* demonstrated capillary HBeAg deposits in two-thirds of the biopsies and the incidence was similar to that reported by Hirose *et al.*

On light microscopyHBV-related membranous nephropathy is characterized by thickened capillary wall and glomerular basement membrane. Immunofluorescent and electron microscopy demonstrate the presence in some cases of viral particles in various locations within the glomerulus,granular IgG, C3 and some IgM in the subepithelial region and the glomerular basement membrane accompanied by abrasionof the podocyte foot processes. Mesangial abnormalities are more common in secondary membranous nephropathy and mesangial expansion and capillary wall thickening resulting in a lobular appearance of the glomerular characterize the light microscopic findings. The capillary wall also demonstrates a double-contour appearance and hypercellularity with interpositioning of cells.In addition to these electron-dense deposits, which could also be present in the subepithelial region, electron microscopy also shows subendothelial expansion and the formation of new basement membrane material. The subendothelial and mesangial immune deposits trigger complement activation and increased local expression of inflammatory and chemotactic mediators, leading to the infiltration of inflammatory cells (Figure 1).

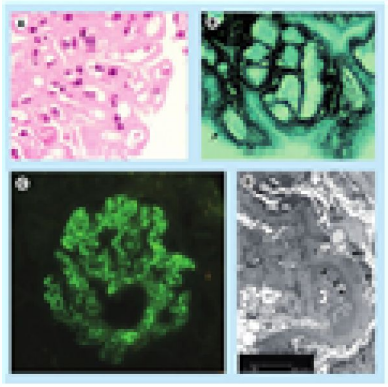

Figure 1.Subendothelial expansion and the formation of new basement membrane material

HBV-related membranous nephropathy clinicaly is different between children and adults. In pediatric subjectsspontaneous remission of proteinuria is common and the renal function is often well preserved. Adult patients are more likely to have progressive disease and up to one third of patients might develop renal failure. Patients with HBV-related membranous nephropathy typically present with proteinuria, which could be in the nephrotic range and microscopic hematuria. Impaired renal function is more common in patients with membranoproliferative glomerulonephritis.A temporal relationship between increased hepatitic activity and deterioration of proteinuria has been observed in some patients and could be associated with cryoglobulinemia.In pathomorphological evidence of HBV-related Mesangial Proliferative GN With Mesangial IgADeposits Lai *et al.* reported the detection of glomerular HBsAg in 30% of renal biopsies from HBsAg holders with IgA nephropathy.

Contrary to the pathologic findings in HBV-related MN, glomerular HBeAg deposits were not detected in the renal biopsies taken from these chronic HBsAg carriers with IgA nephropathy using both polyclonal and monoclonal antibodies. Instead, mesangial deposits of HBsAg similar to the distribution of IgA complexes were detected in 40% and 21% of the renal biopsies suggesting that HBsAg rather than HBeAg may play a pathogenetic role in some of the patients with IgA nephropathy associated with chronic HBV infection.

MCGN is also a well recognized glomerulopathy associated with chronic HBV infection.Simultaneous glomerular deposition of HBeAg and HBsAg in this glomerulopathic entities were documented in many reports of this glomerulopathic entities and are supporting the hypothesis that immune complexes with HBV antigens of different molecular weights could induce a mixed pattern of GN.

Clinical and laboratory findings

Patients withHBC -related Glomerulonephritis have different clinical manifestations. In children there is a strong male preponderance in HBV-related MN and nephrotic syndrome is frequent (Table 1).

Table 1. Clinical presentation of HBV-related membranous nephropathy

From Hepatitis-related Renal Disease Kar Neng Lai Future Virology. 2011;6(11):1361-1376

Characteristic	Children	Adult
Route of HBV infection: Vertical or horizontal within family members Intravenous drug abuse Blood transfusion Sexually	 + - - -	 + (in endemic areas) + (in nonendemic areas) + (in nonendemic areas) + (in nonendemic areas)
Male:female ratio	4:1	2–3:1
History of liver disease	Absent	Absent in endemic areas
Abnormal liver functions	Uncommon	Mild rise in ALT
Presenting symptoms	Nephrotic syndrome	Nephrotic syndrome/proteinuria
Hypertension	<25%	25–40%
Renal insufficiency	Rare	Occasional
Serum positivity for HBeAg and anti-HBc	+ (88.2%)	+ (87.5%)

M

icroscopic hematuria with normal or mildly impaired renal function is rarely present. In adult patients, the most common manifestations is the nephrotic syndrome or isolatedproteinuria. As compared with children, adults are more likely to suffer from hypertension, renal dysfunction and clinical evidence of liver disease.

HBV-related MN has a favorable prognosis in children and high rates of spontaneous remission.Adults with HBV-related MN commonly develop progressive disease. In Hong Kong, for example, up to 29% of patients develops progressive renal failure and 10% developed end-stage renal disease over 5 years. The

prognosis is worser in patients with nephrotic syndrom and HVChepatitis and over 50% of patients requiring renal replacement therapy over 3 years.

For diagnostic purposes and also for estimating response to treatment, laboratory tests including standard liver biochemistries (serum alanine aminotransferase, γ-glutamyltransferase and bilirubin levels) and HBV serologies (HBsAg, HBeAg, anti-HBe and anti-HBc antibodies) should be monitored. HBeAg is present in 80% of patients, who may also have high titers of anti-HBc. Patients should also be tested for circulating HBV DNA levels, and if necessary undergo liver biopsy. In addition, an α-fetoprotein assay could be a useful supplementary diagnostic. Serum C3 and C4 levels must be checked and their level can be low in 20–50% of patients.Light microscopic findings are similar to those of idiopathic MN. The characteristic glomerular lesion is a diffuse thickening of glomerular capillary walls that form thick 'membranes' (Figure 1). This alteration is caused by immune complexes that are accumulated subepithelially. Special stains highlighting the GBM, like methenamine silver and periodic acid-Schiff (PASM or silver stain) or trichrome stain identify slight indentations of the GBM by immune complexes adhering to its surface. Disease progression results in a diffuse thickening of the GBM. The presence of subendothelial deposits, sometimes referred to as MCGN type III changes, increases the probability. that MN is secondary (e.g., HBV-related) rather than idiopathic.The light microscopic define alsoHBV-related mesangialproliferative GN with mesangial IgA deposits as HBV-related mesangial proliferative GN with mesangial IgA deposits. The association between HBV and MN or other forms of glomerular lesion is demonstrated bz the presence of HBV-specific antigens by immunofluorescence.

Treatment of HBV-related GN

The treatment of HBV-related glomerular diseases has been reported to patients with membranous nephropathy, the most common histological presentation. There are no imposing data on membranoproliferative glomerulonephritis or focal segmental glomerulosclerosis secondary to HBV treatment. Hepatologists and nephrologists has to be focused onthe following objectives:

- Liver function normalization and the prevention of HBV-related hepatic complications
- Permanent eradication of HBV
- Treatment of nephrotic syndrome and such complications as hyperlipidemia, edema, infection, hypertension
- Renal function preservation

The administration of immunosuppressive agents and corticosteroids had been previously reported for treatment of HBV-related glomerular diseases in isolated cases, the current view is that such steroids and cytotoxic agents may harm more than they help by causing enhanced viral replication and decomposition.

Actually, antiviral agents have been certified as an important therapeutic option.Treatment with interferon or lamivudine has been reported to lead to a reduction of proteinuria in patients, mostly children. IFN-α is a naturally occurring cytokine produced by B-lymphocytes, lymphocytes and macrophages and possesses antiviral, antiproliferative and immunomodulatory effects. Interferon-α activates cellular pathways that lead to breakdown of viral RNA and enhances cell-mediated immune response toward hepatocytes infected with HBV.

Interferon treatment given for 4–12 months reduced proteinuria in 20% to 100% of patients, clearance of HBeAg in 20% to 80%.

Because the deposition of immune complexes within the glomerulus is perceived to play a pivotal role in the pathogenesis of HBV-related nephropathy, reducing the quantity of viral antigens and reducing immune complex deposition in the kidneysshould ameliorate kidney damage. The treatment of chronic HBV infection has been revolutionizedby the introduction of the nucleoside analog lamivudine. But prolonged treatment with lamivudine may be limited by the drug-resistant strains due to the induction and selection of HBV variants with mutations. An alternative agent that could be considered for use in such lamivudine-resistant cases is adefovir dipivoxil, an acyclic nucleotide analog. This agent is effective against both lamivudine-resistant and wild-type HB.Adefovir should be used with caution in patients with renal impairment in view of its nephrotoxicity.

Unfortunately, as yet there has been no clinical trial regarding its efficacy in the treatment of HBV-related MN nonresponsive to lamivudine treatment.

However, in order to have a reasonable conclusion, clinical trials should fulfill a set of criteria including the results of primary antiviral therapy, the virological response and clinical response as an end point.

Table 2 summarizes nine reports on the therapeutic effect of lamivudine in HBV-related GN. The overall clinical data with lamivudine were better than that of interferon. The link between sustained proteinuria remission and HBeAg clearance was stronger with lamivudine-based studies than interferon-based studies.

Table 2. Characteristics and outcome of published studies on HBV-related glomerulonephritis treated with lamivudine

Country	Patient number (thousand	Age or mean age (yr)	Proteinuria (g/day)	Serum creatinine (mg/dl)	HBeAg	Follow-up (mon)	LAM (mg/day)	LAM duration (mon)	Proteinuria (sustained remission)	HBsAg clearance
Australia	1	6	>300[†]	Normal	Positive	21	100	12	Yes	No
Canada (Vietnamese)	1	5	>3	NA	Positive	6	50	6	Relapse after stopping LAM	No
Hong Kong	10	48 ± 13	4.9 ± 2.4	0.98 ± 0.18	70%	49	100	12	70%	No
Canada (Chinese)	2	44 and 46	7.1 and 8.1	NA	Positive	36	100	12	50%	No
Canada (Chinese)	1	48	3.9	0.76	Negative	36	100	36	Yes	No
Japan	1	37	4.8	GFR 25 ml/min	Positive	108	100	48	Yes	No
Belgium	1	57	4.0	Normal	Positive	25	100	17	Yes	Yes
Taiwan (Chinese)	1	39	4.5	1.4	Positive	9	100	6	Yes	No
Taiwan (Chinese)	1	22	6.0	0.9	Yes	13	100	6	Yes	No
Belgium	1	28	14.5	Normal	Negative	84	100	84	Yes	NA

The associateduse of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and calcium blockers as antihypertensive and renoprotective medications will fulfill antiviral treatment. Future studies on the effect of antiviral therapy on proteinuria or renal survival should include concurrent controls with comparable exposure to these drugs.

In prevention of HBV-related glomerulopathyactive immunization remained the most effective measure. An ideal agent for the treatment of HBV-related glomerulopathy doesn't exist. An effective vaccination program is still far superior to

antiviral treatment despite the promising new antiviral therapies. These medications are expensive and the treatment period and effectiveness is prolonged.

Vaccination for all newborns in some endemic areas has reduced the incidence of chronic HBV infection and its associated complications in children and adolescents. Furthermore, the incidence of HBV-related GN fell by 50% within 10 years of the introduction of a vaccination program in an endemic region. A similar fall in the incidence rate of HBV-related MN was reported in the pediatric population in South Africa. Anyway, the renal prognosis is distinctly different between pediatric and adult patients, with the incidence of chronic kidney disease inHBV-related GNreported as less than 3% in children and up to 30% in adult patients.

Chapter II. Hepatitis C-associated glomerulonephritis

Chronic hepatitis C and renal implication

Clinical manifestations associated with mixed cryoglobulinemiawere first described by Meltzer and col. in 1966. They described palpable purpura, arthralgias and weakness plus variable degrees of GN, lymphadenopathy and hepatosplenomegaly in a selected group of patients. Cryoglobulinemia in these patients had a mixed composition of IgG and IgM rheumatoid factor. The cause of this disease was later association with HCV infection after its discovery in 1989. The most constant and predominant feature of HCV virology is marked by systemic vasculitis, with purpuric skin lesions that showleukocytoclastic vasculitis on biopsy.

Approximately 170–200 million of individuals worldwide have chronic HCV infection. It is obviously known that HCV has a variety of extrahepatic disease manifestations. There are two immunologic features of HCV that may predispose patients to clinicalmanifestations of extrahepatic disease.

First, it is known that HCV provokeimmune aggression, leading to chronic infection and the accumulation of circulating immune complexes expressed by MCGN associated with HCV infection. The second feature is that HCV stimulates production of monoclonal rheumatoid factors.This feature causes type II cryoglobulinemia that is responsible for most of the symptomatic cryoglobulinemic vasculitis.Additionally, nephrologists noted that extrahepatic involvement of chronic HCV infection is responsible for much of the increased morbidity and mortality accompanying the disease.

Cryoglobulinemia is defined as the presence in serum of immunoglobulins that precipitate at reduced temperatures and blood samples obtained from patients for detection of cryoglobulins must be stored and transported at 37°C.

Brouet *et al.* classified three types of cryoglobulins based on their immunoglobulin composition.Type I consists of a single monoclonal Ig without antibody activity and can be found in patients with multiple myeloma, Waldenström's macroglobulinemia or idiopathic monoclonal gammopathy.

Types II and III or mixed cryoglobulins consist of polyclonal IgG and monoclonal IgMκ (type II) or polyclonal IgM (type III) with RF activity. When no definite disease association is found, the condition is referred to as essential mixed cryoglobulinemia. The observation that up to 90% of unselected patients with cryoglobulinemia have anti-HCV antibody indicates that the disease is not genuinely essential, but more likely related to HCV infection. Cryoglobulins consist of

complexes of RF, IgG, anti-HCV antibody and HCV virions. The pathogenesis of cryoglobulinemia due to HCV infection is not well understood, but it appears to be related to excessive proliferation of B cells as a result of the chronic antigenic stimulation of HCV infection.

Mixed cryoglobulinemia (MC) increases with the duration of the hepatitis infection. Chronic cryoglobulinemia occurs in 1% or less of patients, and is usually associated with high RF and cryoglobulin titers.Various histological types of renal diseases are reported in association with HCV infection including membranoproliferative glomerulonephritis, membranous nephropathy, focal segmental glomerulosclerosis, fibrillary glomerulonephritis, immunotactoid glomerulopathy, IgA nephropathy, renal thrombotic microangiopathy, vasculitic renal involvement and interstitial nephritis.

The exact proportion of patients with type I MC who are positive for anti-HCV antibody is unknown.The real prevalence of MC without detectable cryoglobulinemia is difficult to assess. Furthermore, IgM antibodies with anti-IgG activity may induce immune complexes without cryoprecipitable properties. Lastly, these patients may only develop detectable circulating cryoglobulinemia late in the course of the disease.Type 2 MC is associated with chronic HCV infection too.

Initially, the reported cases of MC suggested its association with HBV.However, the role of HCV infection in MC was verified in the 1990s after several cases reported the presence of anti-HCV antibodies and HCV RNA in 70—100% of patients with MC.On the other hand, MC is not seen in all HCV patients; only 10—15% of HCV-infected patients develop MCGN.In a recent study, Lidar and colleagues compared patients with HCV-associated and autoimmune disease—associated MC. Anti-HCV IgG antibodies were detected in all patients with HCV-associated MC but not in any healthy controls, and no anti-HCV antibodies were detected in patients with autoimmune diseaseassociated MC. This finding supports the idea of a possible association between HCV infection and MC.

Cryoglobulinemic GN

The most common type of HCV associated glomerulopathy is type I MPGN associated with type II mixed cryoglobulinemia. If type I MCGN has been regarded as idiopathic for some time, chronic HCV infection is observed in a considerable proportion of patients with type I MCGNaccording to data from the USA and Japan.

The exact proportion of patients with type I MCGN who are positive for anti-HCV antibody is unknown.The real prevalence of MCGN without detectable cryoglobulinemia is difficult to assess.

Furthermore, IgM antibodies with anti-IgG activity may induce immune complexes without cryoprecipitable properties. These category patients may only develop detectable circulating cryoglobulinemia late in the course of the disease.

Type II MCGN (e.g., dense deposit disease) has not been reported in association with HCV infection. MCGN associated with type II cryoglobulinemia is the predominant type of GN clinically associated with HCV infection in studies from Italy, USA and Japan. The prevalence of MCGN in HCV-type II cryoglobulinemia is approximately 30% .In patients with hepatitis C in the absence of cryoglobulinemia MCGN also can be rarely detected.

Renal histological data typically shows evidence of immune complex deposition in glomeruli.MCGN it is a glomerular injury characterized by diffuse mesangial proliferation and thickening of the capillary wall. In cryoglobulinemic MCGN, light microscopy reveals an increased number of mesangial cells, expansion of the mesangial matrixand the interposition of mesangial matrix between the GBM and the endothelium. Immunofluorescence reveals granular deposits of C3 and IgG in the mesangium and in peripheral capillary loops. A similar morphological appearance may be seen with infective endocarditis and infected ventriculoatrial shunts (shunt nephritis). In cryoglobulinemicMCGN glomerular capillaries have marked deposits of inflammatory cell with mononuclear cells and polymorphonuclear leukocytes, a distinguishing feature from noncryoglobulinemic MCGN. Viral HCV-containing antigens can be detected in glomerular structures. Electron microscopy shows subendothelial deposits that may have a distribution suggestive of cryoglobulin deposition. The presence of immunotactoid GN in a viral disease confirms the association of immunotactoid GN with a systemic disease, while fibrillary GN is more frequently a primary disease.

Clinical manifestations

The typical symptoms of HCV-related Cryoglobulinemia are fatigue and palpable purpura, which histologically consists of leukocytoclastic vasculitis (with complexes of anti-HCV antibody and HCV in injured tissue). These lesions can occur anywhere and represent small vessel vasculitis. Patients may have arthritis, Raynaud's phenomenon, fever and neuropathy. Peripheral neuropathy is usually characterized by paresthesias and motor deficit. Abdominal pain arises from mesenteric vasculitis and may mimic an acute abdominal emergency during disease evolution. Hepatosplenomegaly is due to chronic liver disease as a result of HCV. Cryoglobulinemia is more common in women than men and typically occurs after a prolonged period of HCV infection.Patients may have other cryoglobulinemia symptoms, such as palpable purpura and arthralgias.

The typical age of patients withcryoglobulinemic GN is 40–60 years old, and present a mild subclinical evolution of liver disease.

Non-nephrotic proteinuria and microscopic hematuria also might represent a subclinical form of renal involvement in HCV for a long time.

Renal manifestations include nephrotic syndrome in 20% andacute nephritic syndrome in 25%. The clinical course can vary dramatically. Over 80% of patients have severe hypertension which may be a cause for the high rate of cardiovascular deaths and50% of patientswith clinical manifestation develop renal insufficiency. Approximately 15% of patients will require dialysis according to an Italian study. Anyway, HCV-related cryoglobulinemia remains poorly defined and GN tends to have a mild course without significant renal deterioration in the presence of urine abnormalities in the majority of patients.

Laboratory Findings

The diagnosis of HCV-related MCGN is established by laboratory testing . This tests will include biochemical examination like blood for hemoglobin, total count, differential count, ESR. Laboratory investigations like total bilirubin with conjugated and un-conjugated fraction, alanine aminotransferase, aspartate amino transferase, alkaline phosphatase, total protein, albumin,globulin, prothrombin time, HbSAg, Anti nuclear antibody, Anti-Liver Kidney Microsomal antibodies 1, 2 and 3. For assessment of kidney function routine and microscopic examination of urine, 24 h protein excretion and measurement of 24 h urine volume, serum urea, creatinine, serum sodium and potassium have to be examined.

The obtained results need to be coupledwith renal biopsy. A lot of patients are seropositive for anti-HCV antibody and HCV RNA. 70% have raised serum transaminase levels. Cryoglobulins are detected in 50–70% of patients. Serum elec-

trophoresis reveals type II mixed cryoblobulins, in which the RF, almost invariably an IgM is a distinguishing feature of cryoglobulinemic GN. Low or even undetectable levels of the complement components (C4 and C1) is characteristic, while the C3 level tends to remain normal or only slightly reduced.

Treatment of hepatitis C-virus-related glomerulonephritis

Before the association of HCV and cryoglobulinemic MCGN were discovered, the mainstay of treatment was corticosteroids and cyclophosphamide. High dose pulse methylprednisolone followed by oral steroid for months were used to control the evolution of the disease.

Actually, three approaches may be suggested for the treatment of HCV-associated glomerulopathies and cryoglobulinemic renal disease:

1) Antiviral therapy to prevent the direct negative impact of HCV on kidnys and synthesis of immune-complexes

2) B-cell depletion therapy to prevent formation of immune-complexes and cryoglobulins

3) nonspecific immunosuppressive therapy to induce inflammatory cells to prevent the synthesis of immune-complexes and to treat cryoglobulin associated vasculitis

By other authors, two-stage therapy is considered: removal of cryoglobulins by plasmapheresis and the use of corticosteroid/cytotoxic agents or interferon/ribavirin-mediated viral replication suppression.

Controlled trials demonstrate that antiviral therapy with IFN-α improves the systemic symptoms of immune complex disease.However, when short-term interferon monotherapy is used, post-therapy relapse occurs in a large amount of patients. The combination therapy with IFN-α2b plus ribavirin is an important target that improvedconsiderably the evolution of the disease andreduced post-therapy relapses.

Such therapeutical approaches has also produced favorable results in mixed cryoglobulinemia.In some conditions when viral eradication was unsuccessful, long-term maintenance interferon therapy provided the amelioration of the disease.In year 2000 the pegylated forms of interferon (peginterferon) were introduced.

A recent meta-analysis studying 11 clinical trials involving 225 patients revealed that antiviral therapy based onIFN-α can significantly decrease proteinuria and stabilize serum creatinine and therefore, should be indicated in patients with HCV-related GN.

Thus, in patients with moderate proteinuria and stable renal functions, anti-HCV therapy is advised to be started as pegylated interferon-α plus ribavirin. In

patients withnephroticproteinuria and progressive kidney injury immunosuppressive therapy with cyclophosphamide, rituximab should be administrated.

Cyclophosphamide ameliorates the vasculitic injury and inhibits the production of mRFs by B-lymphocytes.For refractory cases, monoclonal antibody against the B-cell surface antigen CD20 (rituximab) has been reported to be effective.

Post-treatment renal biopsy showed histological improvement in two of the three patients who received combination therapy for 12 months.

A lack of this therapeutic approach is the complication of hemolysis in ribavirin therapy, especially for patients with renal impairment.

It is necessary to take glomerular filtration rate into account when determining dosage as well as administering recombinant erythropoietin to overcome anemia.

During the acute phase steroid pulsesandplasmapheresis(three to four times weekly exchanges of 3 l of plasma for 2–3 weeks) can be used. Plasmapheresis are applied to remove circulating cryoglobulins and prevent their deposition in blood vessel walls and glomeruli.

The blockade of the renin-angiotensin system and anti-HCV therapy is preferential in all patients experiencing HCV-related glomerulonephritis and hypertension. The prognosis of HCV-associated glomerulopathies is poor because of a high incidence of cardiovascular diseases and infections.

The optimal antiviral therapy in patients with severe renal insufficiency is not well established. The most recent guidelines from the Kidney Disease Improving Global Outcomes group recommend that clinicians screen, prevent, and treat HCV infection in patients with chronic kidney disease who have no contraindications to antiviral therapy.

Glomerulonephrites due to other hepatitis viruses are rarely identify. Acute nephritic syndrome complicating fulminating hepatitis A infection is casuistically. Pathologies including postinfectious GNhave been reported. Spontaneous remission usually occurs with recovery from the hepatitis. GN has not been reported in hepatitis D or hepatitis E. The future treatment strategy should include: universal vaccination program for endemic areas and populations at risk the use of antiviral agents, including entecavir with appropriate dose adjustment according to renal function.

Chapter III. Tubulointerstitial nephrites and liver disease

Pathophysiology of interstitial nephrites in chronic viral hepatitis

Various types of viral infection have v been reported to induce tubulointerstitial lesions and tubulointerstitial damage is recognized as one of the determinant of the prognosis of hepatitis.

The term of tubulointerstitial refer to kidney diseases that involve structures in the kidney outside the glomerulus. The pathology generally involves tubules and/or the interstitium of the kidney and spare the glomeruli (Figure 2).

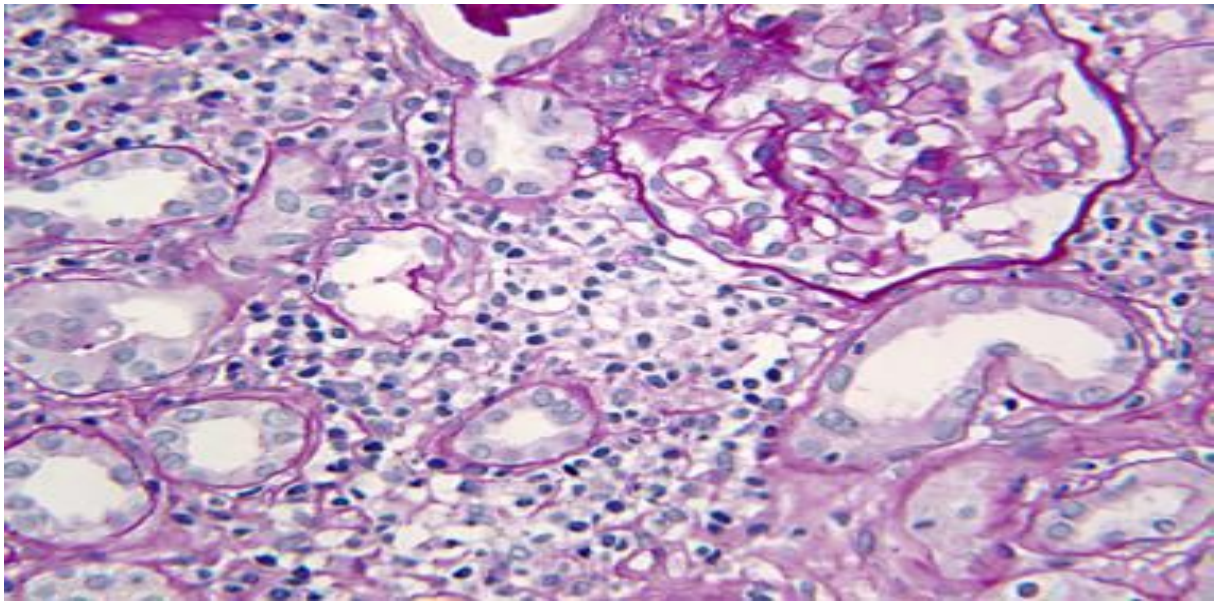

Figure 2.Kidney biopsyof acute interstitial nephritis

The renal cortex shows a diffuse interstitial, predominantly mononuclear, inflammatory infiltrate with no changes to the glomerulus. Tubules in the center of the field are separated by inflammation and edema, as compared with the more normal architecture in the right lower area (periodic acid-Schiff, 40 X).

The initial division of the histologic pattern of tubulointerstitial nephrites (TIN) in viral hepatites is dependent of the presence or absence of a significant inflammatory infiltrate in the interstitium. The structural changes of tubular injury include cytopathic changes from sublethal injury to necrosis, alteration in growth including atrophy, hypertrophy and simplification and the accumulation of cast material in the tubular lumina. Interstitial changes include edema, leukocytic infiltration and fibrosis.

In acute or active forms of hepatic interstitial nephritis the interstitium is edematous and there is a cellular infiltrate that may contain lymphocytes, plasma cells or polymorphonuclear leukocytes. Invasion of the tubules may be seen to resemble the tubulitis of allograft rejection. In more chronic forms, interstitial fibrosis and tubular atrophy is the most prominent feature that may be accompanied by an infiltrate comprised only of small lymphocytes.

Some authors recently has brought attention to a sequence of events where tubulitis eventually leads to tubular destruction and the development of atubular glomeruli. This process contributes both to the histologic picture and the progressive loss of function seen in chronic interstitial nephritis.

Studies in experimental models and in human diseases provide compelling evidence for immune mechanisms of tubulointerstitial disease in hepatitis. These mechanisms are in some instances analogous to immune-mediated glomerular disease involving antibasement membrane antibodies or immune complex deposition. In other instances they are more specific to the structures of the tubulointerstitium and involve antibodies to cell surface antigens, or antigens processed and presented by tubular epithelial or interstitial dendritic cells to the immune system, resulting in cell mediated reactions.

In addition, local activation of epithelial, endothelial and interstitial fibroblastic cells results in expression of a variety of cytokines and growth factors such as platelet-derived growth factor (PDGF) and transformingtumor growth factor-в (TGF-в), which can contribute to inflamation and fibrogenesis in the tubulointerstitial compartment. It has been reported that the sera of patients with chronic HBV infection could induce apoptosis in cultured HK-2 cells, a cell line for the study of human proximal renal tubular epithelial cells.

Furthermore, the induction of apoptosis correlated with the level of circulating HBV DNA, and HBV carriers also showed a higher circulating level of transforming growth factor-beta, a growth factor implicated in the potentiation of apoptosis and renal fibrosis. These preliminary data suggest the presence of serum factor(s) in HBV carriers which could alter renal tubular cell function, and should be confirmed using samples from patients with documented nephritis.

Kasuno K, and al. investigated 320 patients who underwent renal biopsy and did not have extrarenal diseases causing tubulointerstitial nephritis. HCV infection showed a significant association with the prevalence of tubulointerstitial injury. To offset the secondary tubulointerstitial change caused by advanced glomerulopathy, the researchersperformed a glomerular stage-matched comparison of patients withmembranous nephropathy. Comparing areas of interstitial fibrosis and inflammatory cell infiltration, both were greater in HCV-infected than HCV-negative patients. In biopsy tissues from HCV-infected patients, positive signal for HCV was observed in

the perinuclear area of tubular epithelial cells and infiltrating cells on immunohistochemistry,both genomic- and replicative-strand RNA were detected in renal tissues.

Actually, studies have revealed TGF-β as a major participant in fibrogenesis. TGF-β favors accumulation of collagen and noncollagen basement membrane components by direct stimulation of production and by inhibiting matrix degradation enzymes such as collagenases and metalloproteinases. Activation of nuclear transcription factors, such as nuclear factor kappa B (NFκB) in injured kidney cellsn with consequent transcription and release of proinflammatory cytokines into the interstitium, appears to be a major mechanism of chronic tubulointerstitial inflammation accompanying proteinuric liver diseases.

In addition, patients with liver cirrhosis and renal failure frequently are present with lesions that affect other renal structures, such as the vessels. This observation suggests that arteritis could induce ischemic tubular damage in normotensive individuals.Studies of renal pathology in kidney samples obtained by transvenous biopsy are clearly needed to define the real effect of vascular lesions on renal function in patients with liver cirrhosis.

HCV infection is a potent pathogenic factor of tubulointerstitial injury.However, TIN caused by hepatitis C virus remains unclear, although glomerular lesions caused by this viral infection have been well documented.

Clinical features and diagnosis

Patients with TINtypically present with nonspecific symptoms ofmalaise, anorexia or nausea and vomiting. The clinical presentation can range from asymptomatic elevation in serum creatinine or blood urea nitrogen (BUN) or abnormal urinary sedimentto generalized feverand renal failure. Other associated symptoms may include flank pain, gross hematuria or other clinical findings associated with an underlying hepatic disease process.Proteinuria is usually mild, often less than 1 g/d. In contrast to glomerular disease, a significant fraction of the protein is low molecular weight (eg, immunoglobulin light chains, beta2 microglobulin, lysozyme, peptide hormones). These proteins are normally taken up by the proximal tubules and broken down there. Thus, in diseases predominantly involving tubular structures, decreased endocytosis of filtered proteins leads to the characteristic tubular proteinuria.

In addition, the clinical presentation of TIN in hepatitis depends of its severity and renal dysfunction. Despite this factor, certain findings are more common in these patients than patients with glomerular disease.

These include: (1) a lack of significant proteinuria and hypoalbuminemia; (2) the presence of sterile pyuria and white blood cell casts rather than hematuria and red blood cell casts; (3) the absence of a concentration of urine, resulting in polyu-

ria and nocturia.These differences are increasing with the progression of renal failure.

Renal ultrasonography may demonstrate kidneys that are normal or enlarged in size, with increased cortical echogenicity, but there are no ultrasonographic findings that will confirm exactly TIN versus other causes of acute renal failure.

CT has been proposedas a useful test to diagnose TIN. In one small series,nine patients with TIN had positive gallium 67 scans, while six patients with TIN had negative scans. In many studiesother renal disorders such as minimal-change glomerulonephritis, cortical necrosisand TIN in chronic hepatitis have resulted in positive gallium 67 scans. Hemosiderosis or severe liver disease also can result in positive gallium 67 scans.Likewise, patients with biopsy-proven acute tubulointerstitial disease have had negative gallium 67 scans, therefore the predictive value of this test is limited.

In general, patients with TIN have negative scans and in patients who are poor candidates for renal biopsy, gallium 67 scanning may be useful in distinguishing ATN from TIN.

The diagnostic approach to TIN in viral hepatitis is listed in Figure 3.

Renal biopsy is the only definitive method of establishing the diagnosis of TIN; this step usually is undertaken when the diagnosis is unclear and there are no contraindications for the procedure, or when the patient does not improve clinically following discontinuation of the medication suspected as the cause of renal failure. Other laboratory features *(Table 4)* are used to provide suggestive evidence of AIN, to guide conservative management, or to permit empiric treatment with steroids. Unfortunately, none of these tests have sufficient predictive value to be diagnostically reliable. A number of other diagnostic studies have been proposed to help confirm or exclude TIN.

Indications and contraindications for renal biopsy are listed in Table 3.

Table 3.

Indications and Contraindications for Renal Biopsy in TIN and hepatitis

Indications

Acute renal failure from TIN suspected clinically

Exposure to potential nephrotoxic medication

Typical symptoms of rash, fever, arthralgias

Suggestive evidence on laboratory data

No improvement after withdrawal of medication

Patient agrees to procedure

Contraindications

Bleeding

Solitary kidney

Patient unable to cooperate with percutaneous procedure

End-stage renal disease with small kidneys

Severe uncontrolled hypertension

Sepsis or renal parenchymal infection

Patient refusal

Algoritm of diagnosis of AIN in liver diseases

Figure 3.Algorithm for the diagnosis and management of interstitial nephritis. Cruz DN, Perazella MA. Drug-inducted acute tubulointerstitial nephritis: the clinical spectrum Hosp Pract 1998; 33:p.163.

Figure 3 shows an algorithm for diagnosis and management of hepatic patients with suspected AIN.

Treatment of TIN in liver diseases will include the same supportive care as in others TIN:Fluid and electrolyte management, maintenance of adequate hydration and avoiding of volume depletion or overload. Electrolyte abnormalities must be identified and corrected.

Symptomatic relief for fever and systemic symptoms is necessary. Avoid use of nephrotoxic drugs and use of the drugs that impair renal blood flow. Adjust drug dosages for existing level of renal and liver function.

Indications for renal dialysis in the management of acute renal failure have been described elsewhere and these include uncontrolled hyperkalemia, azotemia with mental status changes and other symptomatic fluid or electrolyte derangements.

There are no randomized trials to support the use of corticosteroids in treatment of TIN in liver diseases. Small case reports and studieshave demonstrated rapid diuresis, clinical improvementand return of normal renal function within 72 hours after starting steroid treatment, although some case reports indicate lack of efficacy.

If steroid therapy is started, a reasonable dosage is prednisone, 1 mg per kg per day orally (or equivalent intravenous dose) for two to three weeks, followed by a gradually tapering dose over three to four weeks. In patients who do not respond to corticosteroids within two to three weeks, treatment with cyclophosphamide (Cytoxan) can be considered.Antiviral therapy with IFN-α improves the systemic symptoms of tubulointerstitial nephrites.

Chapter IV.Glomerulopathy associated with liver cirrhosis

Pathophysiology of glomerulardisfunction

An association between glomerular disease and liver cirrhosis has been known since the 1950s although early autopsy studies did not take account of viral infection, bacterial sepsis and other factors that might also provoke glomerular injury. Glomerular changes in cirrhosis of the liver are usually related to the liver dysfunction, although de novo glomerulonephritis may occur**.**Glomerular lesions are reported in more than 50% of cirrhotics and this rises to 100% in studies of end-stage liver disease.

Although minor glomerular damage and mesangial proliferation are common, a range of other light microscopic changes have been described in cirrhosis. Membranoproliferative glomerulonephritis, membranous glomerulonephritis and focal segmental glomerular sclerosis are the most common causes of intrinsic renal disease in patients with hepatitis C. Membranous nephropathy is most prominent in patients with hepatitis B, whereas immunoglobulin A nephropathy is most often seen in patients with alcoholic cirrhosis. A kidney biopsy in the evaluation of renal failure in cirrhosis of unclear etiology may be useful.

The first described abnormalities included a fibrillar thickening of the mesangial stalk and of the basement membrane of the capillary loops. Immunofluorescenc have shown that the mesangial deposits contain immunoglobulins, in particular IgA. These changes were reported in about half of all cases of liver cirrhosis coming to necropsy. Autopsy studies have reported glomerular abnormalities in most patients with posthepatic or alcoholic cirrhosis.

Thisglomerulonephritis could be related to hepatitis C or hepatitis B antigens. Cryoglobulinemiacomplicating hepatitis C infection may induce immune complex glomerulonephritis. However, these antigens are neither frequently found in liver cirrhosis nor is cryoglobulinemia commonly seen in hepatitis-C positive patients.

The light microscopic features of cirrhotic IgA nephropathy are similar to primary IgA nephropathy. There is a variable widening of mesangial matrix, thickening of the capillary wall, mesangial hypercellularity, usually diffuse and sometimes segmental, with mesangial electron-dense deposits. Occasionally, a mesangiocapillary pattern is seen and rapidly progressive GN has also been described. Mesangial IgA predominates but is often associated with lesser amounts of IgG, IgM, or C3. As in primary IgAN, mesangial IgA may be seen in the absence of light microscopic changes. Ultrastructural features may, however, be distinctive: mesangial

interposition and splitting of the GBM are more commonly seen than in primary IgA nephropathy.

It is interesting to note that glomerulonephritis has also been described in alcoholic hepatitis and in viral hepatitis without cirrhosis.It is probable that IgA produced by intestinal plasma cells interacts with food antigens that cross-intestinal mucosa damaged by alcohol and induce formation of immune complexes. In some studies, immune dysfunction has been induced in the mucosal immune system by infusion of liquid diet containing alcohol, which led to IgA nephropathy.

Furthermore, the chronic use of alcohol and duration of its administration has been linked to incidence of glomerulonephritis in liver cirrhosis.Serum levels of IgA were high in 77 to 91 percent of patients and it was due to the increased synthesis of antibodies to bacterial and dietary antigens.

In cirrhotic patients with portocaval shuntsand impaired liver catabolism of polymeric IgA and immune complexes there were demonstrated higher levels of IgA.

Additionaly,igh IgA levels in alcoholic cirrhosis was caused by the increased synthesis of IgA by peripheral lymphocytes in addition to decreased catabolism. Complement C3 levels may be low in these patients. No correlation has been observed between hypocomplementemia and the degree of liver dysfunction.

There are two main recognized patterns - glomerulopathy without proliferation and glomerulonephritis with proliferation. Electron microscopy reveals electron dense deposits that are mainly mesangial but frequently extend into the subendothelial space. IgA is the main immunoglobulin in glomerular deposits, although IgG and/or IgM may co-exist.

The glomerular changes of 50 autopsy cases of liver cirrhosis of different etiologies, such as alcohol abuse, HB virus infection, and nonA–nonB virus infection, were studied by light, immunofluorescence and electron microscopy. The glomerular changes observed were as follows; membranoproliferative glomerulonephritis (MPGN) type 1 (7 cases), mild form or early stage of MPGN type 1 (7 cases), mesangial proliferative glomerulonephritis with sub–endothelial deposits (13 cases) and mesangial proliferative glomerulonephritis without subendothelial deposits (12 cases). These glomerular changes were frequently accompanied by predominant IgA deposition (78% of the immunofluorescence positive cases). Minimal glomerular changes without electron dense deposits were present in 11 cases, in which IgA was not found in the glomeruli. The authors consideredthat pathophysiological condition of liver cirrhosis reduced phagocytic activity of the reticuloendothelial system of the cirrhotic liver as a major factor for the development of these glomerular changes.

There have been no direct studies of the mechanism of mesangial IgA deposition in hepatic cirrhosis. The presumption that the mesangial deposits represent IgAhas not been directly confirmed and there are no sufficient studies reliably identifying antigens within the mesangial deposits.

Clinical and diagnostical approaches to cirrhotic nephropathy

Intrinsic renal disease in liver cirrhosis is considered if there is proteinuria > 500 mg in 24 hours, abnormal urine sediment with >50 red cells and abnormal renal ultrasound findings in the absence of other causes of renal failure. Gross hematuria may rarely occur.Therefore, routine urine examination for proteinuria and hematuria should always be done in search of possible glomerulopathy. Cirrhotic nephropathymay be clinically silent and is usually asymptomatic.

Rarely patients can present with nephrotic syndrome and renal failure. One consecutive study in cirrhotics indicated that 9.6% of cirrhotics have anephritic urine and 1.6% are nephrotic.Patients with MPGN or endomesangial proliferation can be present with nephrotic range proteinuria.

The severity of urinary sediment correlates with the severity of the glomerular lesions and degree of mesangial cell proliferation.

Cirrhotic nephropathy is frequently static and only rarely it can progress to end-stage renal failure. No correlation has been found between the severity of liver failure and the manifestation of the glomerular disease. These abnormalities may be moderate or severe as assessed histologically, it is unusual to see clinical evidence of glomerulonephritis because the changes are largely confined to the mesangium.

Patients with endocapillary proliferation present clinically with features of acute glomerulonephritis, whereas those with membranoproliferative changes have either proteinuria or microscopic hematuria or have no urinary abnormalities.

Detection ofarterial hypertension in patients with cirrhosis of the liver should raise suspicion of underlying glomerular disease because hypertension is not common in liver cirrhosis.

Circulating immune complexes and antibodies against viralantigens can be found. Immune complexes are mainly IgA (IgA1 and IgA2 subclasses). Similarly mixed cryoglobulins have also been present,although correlation between these antibodies and glomerulonephritis was not yet establish.

Treatment of glomerular disease in liver cirrhosis

There is no traditional treatment for hepatic glomerulophathy and the prognosis of the disease depends on the progression of the cirrhosis.

On the other hand, there is no consistent evidence that improvement in the hepatic disease improves the renal disease.Some biopsy data suggest that the glomerular disease usually don’t change morphologically over a number of years.Treatment therefore is symptomatic. Adequate control of blood pressure by angiotensin converting enzyme inhibitors is advised.

Additionaly, if proteinuria is below 1 g/24 hours, patients should be just observed with symptomatic treatment. If proteinuria exceeds 3 g/24 hours and the GFR is in the limits of normal a course of prednisolone (60 mg pe day) may be tried.

Chapter V. Current approach to renal failure in patients with liver cirrhosis

Causes of renal failure in cirrhosis

1. **Drug toxicity**

Renal failure in patients with cirrhosis was initially described as renal dysfunction characterized by progressive azotemia associated with marked abnormalities of the systemic and renal arterial circulation . Patients with liver cirrhosis are more susceptible to the development of progressive renal failure. Actually, it is known that patients with cirrhosis can develop renal failure for a variety of reasons besides hepatorenal syndrome (HRS), including bacterial infections, shock, the use of nonsteroidal anti-inflammatory drugs, antibioticsand intrinsic renal diseases.Impaired glomerular filtration plays a major role in the pathophysiology of a large number of complications seen in patients suffering from liver diseases.

Azotemia is found in 30% of patients with liver cirrhosis and ascites. Acute renal failure can be caused by nonspecific infection in 32%, renal parenchymal disease in 24%, hypovolemic shock in 22%, acute tubular necrosis (ATN) in 11%, hepatorenal syndrome in 8% , acute renal failure (ARF) from drug toxicity in 3%.The mortality as a result of renal complications is significantly higher, ranging from 50 to 70% in ATN and 75 - 100% in HRS.

Evidence accumulated during the past few years suggests that in decompensated cirrhosis, renal function is dependent of renal prostaglandin synthesis. Inhibition of prostaglandin synthesis by non-steroidal anti-inflammatory drugs induces acute reversible reductions of renal blood flow and glomerular filtration rate. Furthermore, it has been documented that renal synthesis of vasodilator prostaglandins, such as prostaglandin E2(PGE2) and prostacyclin, is decreased in those patients with preserved renal function and is accompanied by reductions in urinary prostaglandins.

In addition, body immersion in water up to the neck in patients with decompensated liver disease causes a significant natriuresis, increased GFR and increased the urinary excretion of PGE-2 about three times. Rincon-Sanchez A. et al. evaluated the effect of infusion of PGE-2 on liver and kidney function in experimental cirrhosis models. Cirrhotic rats were exposed to a dose of carbon tetrachloride for eight weeks. Intramuscular injection of PGE-2 decreased acute phase of inflammation mediatores (acidglicoprotein Alpha-1, fibrinogen, Apo-A1M RNA-protein) in serum and improve liver and kidney function.

Cirrhotic patients are also at risk of aminoglycoside nephrotoxicity. In one study involving patients with liver cirrhosis and infection who were treated with an aminoglycoside antibiotic, the prevalence of acute tubular necrosis was 30% and urinary levels of β2-microglobulin, as a marker of tubular damage were highly increased.Other nephrotoxic antibiotics such as oral neomycin given for hepatic encephalopathy can also cause renal failure.A low incidence of nephrotoxic effects was associated with the administration of contrast agents.

Additionally, aggressive use of diuretics is a common cause of renal impairment in cirrhosis. Two types of renal failure occur in diuretic-treated patients with cirrhosis. The first occurs in patients who continue diuretic treatment after complete resolution of ascites. If their diuretic dosage is not reduced, these patients develop renal impairment associated with dehydration and hypovolemia. The second type is observed in patients with ascites. Ascitic fluid is reabsorbed through peritoneal stomas connected to lymphatic vessels under the diaphragmatic surface of the peritoneum. The quantity of ascites reabsorbed varies from patient to patient (<250 ml to >4l daily). If the diuretic-induced increase in urine volume is more than the body's maximum reabsorption capacity of ascites, hypovolemia and renal failure develop.

2. Non-specific Infections

Bacterial infections represent a common complication in patients with cirrhosis and ascites, Recent studies also confirms that urinary tract infections, pneumonia, and spontaneous bacterial peritonitis (SBP) represent the most common type of bacterial infection in patients with cirrhosis and ascites. According to the criteria of the American College of Chest Physiciansbacterial infection was associated with a diagnosis of sepsis, therefore defining a picture of sepsis in 37.9% of cases. The development of bacterial infection in patients with cirrhosis and ascites is associated with higher in-hospital mortality as observed by Foreman et al., and a longer hospital stay. The lack of resolution of the bacterial infection and MELD score, were the only predictors of death among a large series of parameters which were analyzed at the diagnosis of bacterial infection.

Spontaneous bacterial peritonitis, a infection of ascitic fluid without a definitive intra-abdominal source is a most common complication in patients with cirrhosis and ascites. Patients with ascites who have been followed prospectively for one year have a 10% to 25% incidence of having at least one episode of SBP during that time period. When patients with ascites underwent routine paracentesis, the incidence of active SBP ranged from 10% to 27% .

The prognosis is generally improved if antibiotics are begun before the onset of shock and renal failure. Patients who develop renal dysfunction at the time of active infection have the highest mortality

The study ofFollo A, Llovet JM, and alt.was assessed to show the incidence, clinical course, predictive factors and prognosis of renal impairment in cirrhotic patients with peritonitis. Therefore, 252 consecutive episodes of spontaneous bacterial peritonitis in 197 patients were analyzed. Renal impairment occurred in 83 (33%) episodes, and in every instance it fulfilled the criteria of functional kidney failure. Renal impairment was progressive in 35 episodes, steady in 27 and transient in 21 and was the strongest independent predictor of mortality during hospitalization. Other independent prognostic factors were blood urea nitrogen level before peritonitis, age, positive ascitic fluid culture and serum bilirubin level during infection. These results indicate that renal impairment is a frequent event in cirrhotic patients with spontaneous bacterial peritonitis that occurs mainly in patients with kidney failure before infection.

Other investigations concluded that one-third of patients with cirrhosis and SBP develop renal failure despite rapid resolution of the infection with antibiotics. In 30% of these patients renal failure is transient, in 25% it follows a steady course with unchanging severity and in 45% a rapidly progressive failure develops.

The prevalence of rapidly progressive renal failure in patients with other infections is considerably lower. Progressive renal failure occurs in 15% of patients with acute pyelonephritis. Patients that responde to antibiotic treatment develop only transient renal failure.

The reason why SBPis associated with such a high incidence of renal failure is that an exaggerated inflammatory response to sepsis occurs in patients who have decompensated cirrhosis with ascites. This occurs in the context of increased serum levels of cytokines (TNF, interleukin-6) of nitric oxide and other endogenous vasodilators. In cirrhotics, the increase in plasma levels of these cytokines after sepsis is more greater than in individuals without cirrhosis, and persists for a longer duration. In support of this contention, patients with SBP who have increased serum creatinine levels or dilutional hyponatremia before infection, and those who have an intense inflammatory response (high concentrations of polymorphonuclear leukocytes and cytokines in ascitic fluid) at diagnosis of SBP, are at high risk of developing renal failure.

3. Prerenal azotemia

In patients with cirrhosis and upper gastrointestinal bleeding, the incidence of renal failure is 11%. Risk factors for renal failure in this case include the severity of blood loss (the prevalence of renal failure in patients with and without hypovolemic

shock was 60% and 5%, respectively).In the presence of decompensated liver cirrhosisthe prevalence of renal failure was 29% in patients with Child-Pugh class C versus 3% in classes A and B.

Patiens are usually symptomatic and have already developed some complications of the disease, the reduction in systemic vascular resistance is marked and cannot be compensated by further increases in cardiac output. Therefore, underfilling of the arterial circulation develops, there being a disarrangement between the intravascular blood volume and a very enlarged intravascular arterial circulation. This condition is known as effective arterial hypovolemia.Hypovolemia unloads the high-pressure baroreceptors in the carotid body and aortic arch with compensatory activation of the sympathetic nerves system (SNS), the renin-angiotensin-aldosterone system (RAAS) and nonosmotic release of vasopressin. This results in a hyperdynamic circulation with increased cardiac output, decreased systemic vascular resistance, hypotension, and vasoconstriction of the renal vessels.

Patients, who developed renal failure caused by bleeding recover their renal function ofter volume repletion. This confirms that the etiology of their kidney dysfunction is prerenal azotemia. However, in patients with TINor HRS, renal failure persists or progresses despite resolution of the bleeding episode and volume repletion.

In addition, patients with cirrhosis and renal failure frequently present lesions that affect other renal structures, such as the vessels, tubules and interstitium. This observation suggests that arteritis could induce ischemic tubular damage in this category of patients.

4. Hepatorenal syndrome

Hepatorenal syndrome is a unique form of severe functional kidney failure due to intense renal vasoconstriction that develops in patients with hepatic cirrhosis in the absence of significant histological abnormalities of the kidneys.

A recent studyhas revealed that hepatorenal syndrome is the third most common cause of admission to hospital in the intensive care unit among 420 patients with cirrhosis and was only surpassed by upper digestive hemorrhage and encephalopathy. Mortality occurred within one to five years in 69% to 77% of all these patients.

Intermediate forms of HRS occur commonly in acute liver failure or chronic liver disease and two main patterns of HRS can be identified:

Type 1 HRS - rapidly progressive, where serum creatinine doubles in two weeks and values ofapproximately 350 μmol/L (2.5 mg/dL) are usually achieved.

This type accompanies clinically more serious conditions and it is typically unstable. Its main clinical feature is acute renal failure or a 50% reduction of the initial 24-hour creatinine clearance to a level lower than 20 ml/minute in less than two weeks.It is associated with the development of oliguria, encephalopathy and marked hyperbilirubinemia.

Type 1 HRS usually occurs in closerelationship with a precipitating event, mainly spontaneous bacterial peritonitis. Other infections and noninfectious events (such as viral, alcoholic, toxic or hepatitis superimposed on cirrhosis; gastrointestinal bleeding and major surgical procedures) are less frequently associated with HRS. However, in some patients with type 1 HRS, a precipitating event cannot be identified. Episodes of spontaneous bacteremia owing to translocation of bacteria from the intestinal lumen into the systemic circulation, as well as translocation of bacterial endotoxins are frequent in patients with liver cirrhosis and may act as precipitating factors.

Most patients with type 1 HRS had severe liver cirrhosis characterized by a MELD score ≥ 20 or Child Pugh score ≥12. The syndrome is frequently diagnosed in acute fulminant hepatic failure or alcoholic hepatitis. Jaundice and coagulopathy, bleeding from esophageal veins is frequently present. Patients with severe alcoholic hepatitis have a higher probability of association of sepsis in the case of type 1 HRS installation and high rate of mortality, eloquently demonstrated by a study conducted on a group of 195 patients. In the absence of liver transplantation (LT), the mean survival rate of patients with HRS type 1 is about two weeks, most patients with a fatal end within 2-3 months from the establishment of the diagnosis. There was an average survival rate of 2.7 months in 91 patients with type 1 HRS in a retrospective study of cirrhotic patients with HRS in 24 medical centers in Europe,

Type 2HRS is slowly progressive, this state was described later and despite the otherwise typical signs of hepatorenal failure, it is quite stable. It is characterized by impairment in renal function (serum creatinine - 415 µmol/l) that does not have a rapidly progressive course and does not meet the criteria of type 1 HRS. The typical clinical self-evidence of Type 2 HRS is the presence of refractory ascites in patients with liver cirrhosis due to a poor response to diuretics (furosemide and spironolactone) and sodium retention. The median survival after onset of type 2 HRS is 6 months. Type 2 HRS is associated with stable or slowly progressive kidney failure and has a better prognosis than HRS type 1.

In type 2 HRS and in some patients with type 1 HRS, no precipitating factor can be identified. The mechanism of renal failure in these cases is unclear, but it seems to be related to severe failure of compensatory mechanisms of liver disease that aim to maintain adequate renal perfusion. The main precipitating factors of HRS are illustrated in Figure 4.

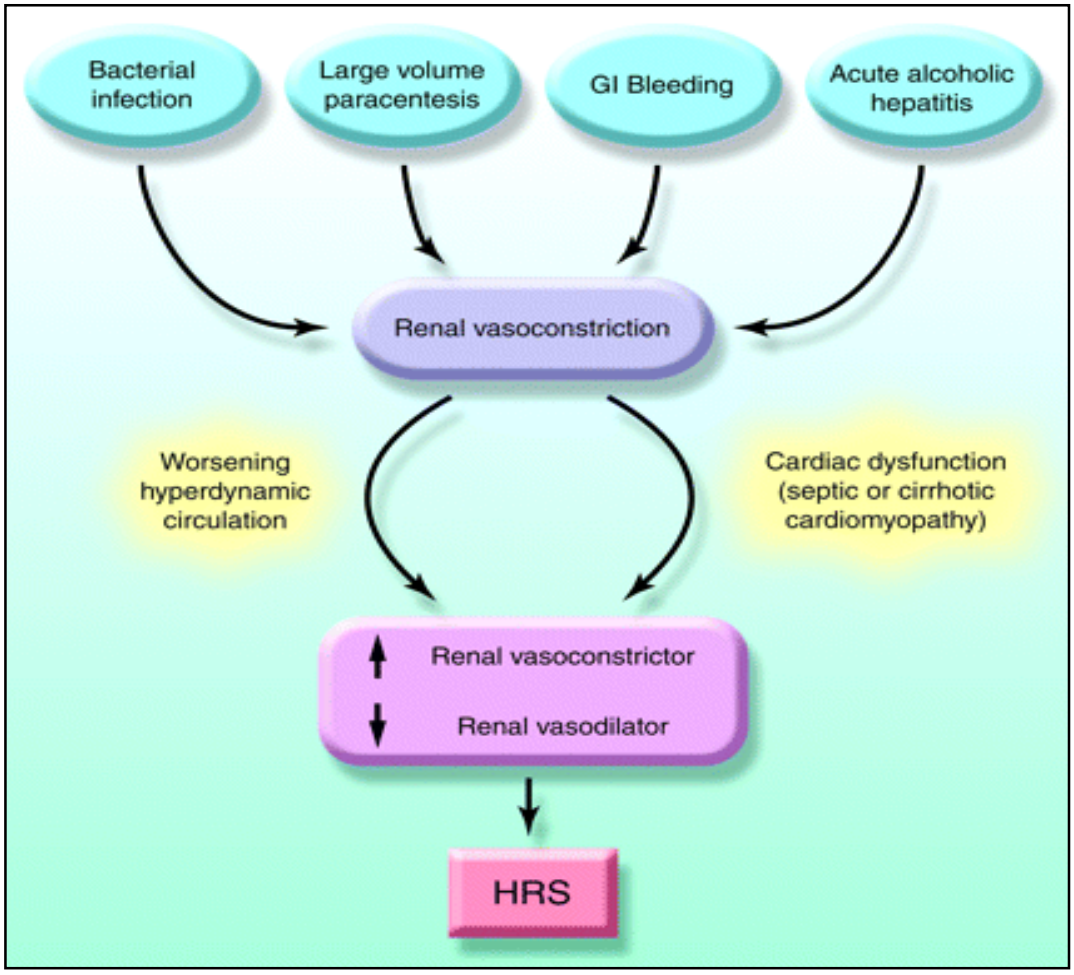

Figure 4. Precipitating factors in HRS (Hani M. Wadei, Martin L. Mai, Hepatorenal Syndrome: Pathophysiology and Management CJASN September 2006 vol. 1 no. 5 p.1066-1079).

Renal failure in liver cirrhosis is multifactorial and can present as pre-renal or intrinsic renal dysfunction. Obstructive or post renal dysfunction only rarely complicates liver disease (Table 4).

Table 4. Main causes of renal failure in patients with liver cirrhosis

Infections
Spontaneous bacterial peritonitis
Urinary tract infection, pneumonia, skin infection, or any other bacterial infection
Hypovolemia-induced renal failure
Gastrointestinal bleeding (with or without shock)
Diuretic-induced
Vomiting and diarrhea
HRS
Intrinsic renal diseases
Glomerulopathies due to viral hepatitis
Acute tubular necrosis: aminoglycosides, amphotericin B, or tenofovir
Acute interstitial nephritis: penicillin, rifampin, or sulfonamides
Drug-induced renal failure
Chronic kidney disease ,including diabetes, hypertension, or other causes

Chapter VI. Diagnostic approach toacute kidney injury inliver cirrhosis

Actually, the gold standard for measuring the glomerular filtration rate in cirrhosis is based on clearance techniques of markers as inulin or cistatin C. However, these methods are expensive, and not widely available in all settings. The assessment of serum creatinine concentration in renal dysfunction of liver cirrhosis is wellknown, but could be not sufficiently informative.

Recently, novel biomarkers for diagnosing tubular damage in patients with liver cirrhosis and HRS are in quest.

Several studies have demonstrated the utility of early measurement of urinary enzymes for predicting the severity and clinical outcomes of liver disease.Limited data indicate that urinary neutrophil gelatinase-associated lipocalin, a urinary biomarker is useful in discriminating between HRS and intrinsic renal failure (acute tubular necrosis).

However, data on biomarkers in the assessment of renal failure in cirrhosis are insufficient and this approach to diagnosis cannot yet be routinely recommended.

Renal failure in cirrhosis is established when SCr increases more than 1.5 mg/dL. New attempts at defining renal failure in cirrhosis using the definition of acute kidney injury have been proposed.

AKI in cirrhosis is defined as an increase in SCr > 50% from the baseline or a rise in SCr ≥ 0.3 mg/dL in <48 hours(Table 5). This definition has the advantage of detecting earlier phases of kidney dysfunction with the goal of implementing early intensive therapy.

Table 5. Proposed AKI Diagnostic Criteria in Cirrhosis (*Gut*. Copyright 2011, British Society of Gastroenterology).

Diagnosis	Definition
AKI	Rise in SCr ≥ 50% from the baseline or rise in SCr ≥ 0.3 mg/dL in <48 hours
Chronic kidney disease	GFR < 60 mL/minute for >3 months (calculated with the MDRD6 formula*)
Acute-on-chronic kidney disease	Rise in SCr ≥ 50% from the baseline or rise in SCr ≥ 0.3 mg/dL in <48 hours in a patient with cirrhosis and a GFR < 60 mL/minute for >3 months

The most important step in treating renal failure in a patient with liver cirrhosis is to identify its etiology.There are no specific tests that help to tease out the different causes of renal dysfunction in patients with cirrhosis. In the majority of cases, a detailed clinical history, a physical examination and an estimation of renal function with the evaluation of urine and serum electrolytes will be sufficient for establishing the cause.

Because the diagnosis of HRS cannot be made with a specific test, its confirmation is currently made with criteria excluding other causes of renal failure that can occur in cirrhosis.A diagnostic algorithm is depicted in Fig.5

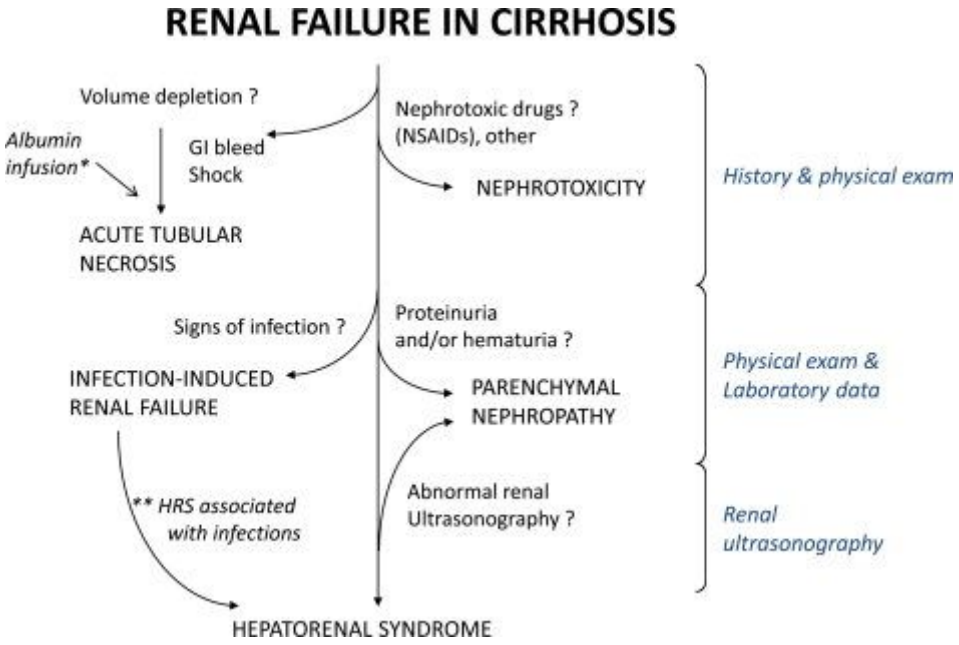

Figure 5. Diagnostic algorithm for patients presenting with renal failure and cirrhosis. (Adapted with permission from *Lancet*.Copyright 2003, Elsevier).

The parameters traditionally used to differentiate acute tubular necrosis from functional renal failure have no value in patients with cirrhosis and ascites. Granular casts might be present in the urinary sediment of patients with both HRS and acute tubular necrosis and are therefore also unhelpful in distinguishing between these two conditions.

The criteria for diagnosis of acute renal failure and to differentiate prerenal azotemia, acute tubular necrosis and HRS are shown in Figure 5,Table 6, 7.

Table 6. Criteria for diagnosis of acute renal failure - prerenal azotemia and acute tubular necrosis

(Christos P. Carvounis, Sabeeha Nisar and Samerah Guro-Razuman.Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. Kidney International (2002) 62. p.2223–2229).

A. Acute renal failure
1. Azotemia—rapidly increasing BUN and creatinine (BUN>30 mg/dL and creatinine>1.5 mg/dL) with or without oliguria.
2. Serum creatinine increase in excess of 0.5 mg/dL in the preceding 2 days.
B. Criteria to differentiate ATN from prerenal azotemia
1. History (volume depletion, decreased cardiac output or vasodilation related to sepsis, liver failure and anaphylaxis favor prerenal azotemia, while exogenous toxins such as medications, or endogenous toxins as in the case of myoglobin, or even prolonged renal hypoperfusion that became unresponsive to appropriate corrective measures or to high dose of loop diuretics).
2. Physical examination (blood pressure, heart rate, orthostatic changes, cardiac sounds, pulmonary findings, presence of ascites or leg edema).
3. Findings of the urine analysis (urinary sediment undetected in prerenal failure, presence of muddy brown granular casts in patients with ATN). Response to therapy also was recorded.
4. Urinary indices evaluated at the time of consultation are:
—Urinary sodium (U_{Na}): U_{Na} <15 mEq/L favors prerenal failure, while a value higher than 20 is consistent with ATN.
—Urinary to plasma creatinine ratio (U/P_{Cr}). U/P_{Cr}>20 is consistent with prerenal while levels <15 suggest ATN.
—Fractional excretion of sodium (FE_{Na}). FE_{Na} <1% is suggestive of prerenal azotemia, while levels>1% indicate the presence of ATN.
—Urinary sodium/potassium ratio (U_{Na}/K; a reflection of prerenal conditions with associated hyperaldosteronism). If U_{Na}/K is less than $^1/_4$, this favors prerenal azotemia.

Table 7. Differential diagnosis of ARF in advanced liver disease

(Miller T.R, Anderson R.J, Linas S.L, et al: Urinary diagnostic indices in acute renal failure. Annals of Internal Medicine 1978.89.1,p. 47–50).

Indices	**Prerenal failure**	**Intrinsic renal failure**	**HRS**
Urine sodium	< 10	> 30	< 10
U/Pcreat	> 30:1	< 20:1	> 30:1
U/Posm	UO > PO	UO = PO	UO > PO
Urine sediment	Normal	Casts, cellular debris	Unremarkable
History disease	Profound volume	Volume contraction	Advanced liver disease
Clinical course (renal response)	Contraction	Nephrotoxic agent sepsis	Tense ascites
Fluid challenge	+	-	-
Vasoconstriction	±	-	+

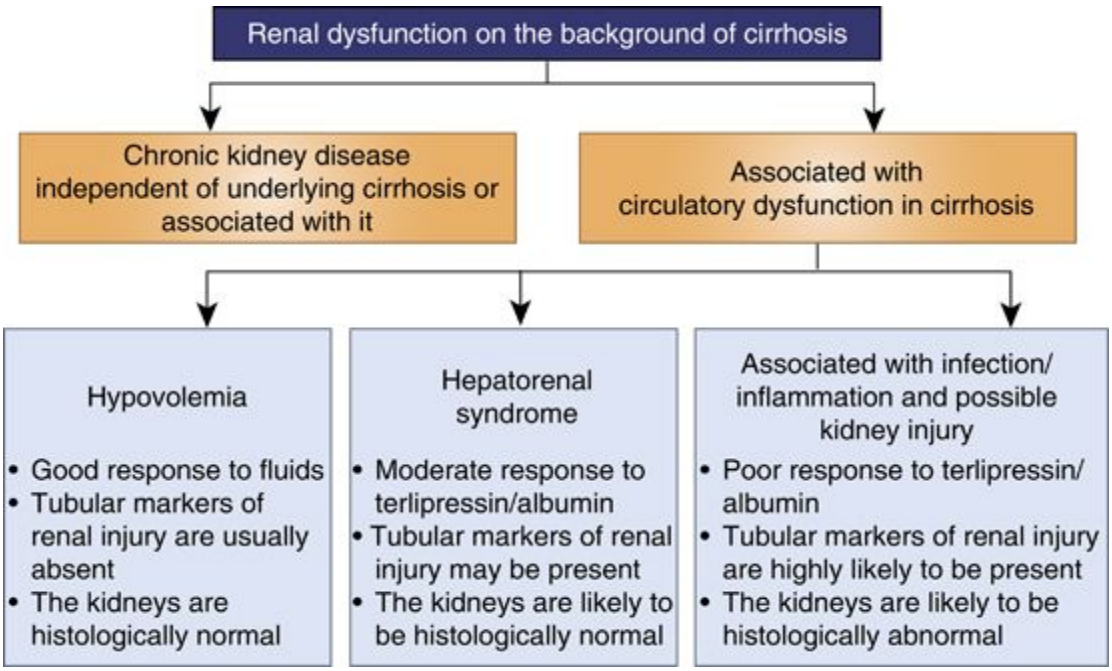

Figure 6. Differential diagnosis of renal dysfunction in liver cirrhosis (Adebayo D et al. Renal dysfunction in cirrhosis is not just a vasomotor nephropathy. Kidney International2015. 87, p. 509–515).

Due to the lack of specific biochemical or radiologic markers, the diagnosis of HRS is based on criteria to exclude other causes of renal impairment that may be found in liver cirrhosis. The criteria defined by the International Ascites Club (by Arroyo V, et al, 1996) are listed as follows:

Major criteria:

Chronic or acute liver disease with severe hepatic insufficiency and portal hypertension.

Reduced glomerular filtration rate, defined as serum creatinine > 1.5 mg / dL or lower creatinine clearance <40 ml / min.

Exclusion of the shock, bacterial infections, fluid losse, treatment with nephrotoxic drugs (nonsteroidal anti-inflammatory, aminoglycosides, etc.).

Exclusion of excessive fluid loss in the digestive system (vomiting or diarrhea) or renal function (weight loss over 500 g/day for several days, in patients with liver cirrhosis and ascites, edema).

Improves renal function (serum creatinine falls below 1.5 mg / dl, creatinine clearance 24 hours does not increase above 40 ml / min) after discontinuation of the diuretic and given 1500 ml of solution.

Proteinuria <500 mg / 24 hours, indicating the absence of sonographic criteria obstructive or parenchymal renal disease.

Minor criteria:

Diuresis <500 ml / 24 hours.

Urinary sodium <10 mEq / l.

Urinary osmolarity> plasma osmolarity.

Urinary red blood cells <50 / field.

Serum sodium <130 mEq / l.

New diagnostic criteria of HRS

Due to the non-specific additional criteria (they can be found in patients with acute tubular necrosis and may be absent in patients with SHR and hyperbilirubinemia) these criteria were conflicting for the diagnosis of SHR.

In 2007, in town San Francisco at the 56th meeting of the American Association for the study of Liver Diseases and the International Ascites Club to reach a consensus, criteria for diagnosis of SHR were reviewed (Table 8).

Table 8. New diagnostic Criteria of HRS (after Salerno F, et al, 2007)

1. Cirrhosis with ascites.
2. Serum creatinine >1.5 mg/dL (>133 μmol/L)
3. No improvement in serum creatinine level (decrease to >1.5 mg/dL (>133 μmol/L]) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is a single infusion of 1 g/kg of body weight(maximum 100g)
4. Absence of shock
5. No current or recent treatment with nephrotoxic drugs
6. Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/d, microhematuria (>50 red blood cells/high-power field), and/or abnormal renal USG

Conclusions

- Chronic liver disease involves a process of progressive destruction and regeneration of liver parenchyma leading to fibrosis and cirrhosis. The evaluation of numerous exogenous and endogenous measures of kidney involvement in liver diseases continue to be the focus of research in different patient population . Many aspects of these problems remain unclear and will continue to be an important issue as clinical research in hepatology and nephrology.
- Chronic HBV and HCV infection are resulting in hepatic and extrahepatic complication, including glomerulopathy. Renal biopsy with molecular testing is essential for the diagnosis of virus-related glomerular lesions and providing prognostic and therapeutic guidance. Antiviral agents remain the mainstay of treatment.
- Various types of viral infection have been reported to induce tubulointerstitial lesions and tubulointerstitial damage is recognized as one of the determinant of the prognosis in evolution of hepatitis. HCV infection is a potent pathogenic factor of tubulointerstitial injury, too.
- Renal failure in cirrhosis is multifactorial and can present as pre-renal or intrinsic renal dysfunction. Patients with severe liver dysfunction can develop HRS, ATN that are characterized by a marked reduction in renal blood flow and severe hemodynamic disturbances.
- In clinical practice plasma creatinine level and endogenous creatinine clearance are commonly used as more convenient but less accurate method for glomerular filtration rate in liver cirrhosis. Current scientific research is focused on the identification of novel diagnostic biomarkers of renal failure in hepatic diseases.
- Crucial innovations in diagnosis and management of renal impair will facilitatethe earlier viral treatment, which may lead to decrease the morbidity and mortality.
- The future treatment strategy should include universal vaccination program for endemic areas and populations at risk and the use of newer antiviral agents.
- The importance of a nephrologist in the multidisciplinary management of patients with renal abnormalities in liver diseases cannot be overemphasized. Nephrologists assist hepatologistsin the management of these difficult treated patients.

Clinical approach considerations

1. In patients with TIN secondary to liver diseases proteinuria is usually absent or modest. Urinalysis may show microscopic hematuria and/or sterile pyuria. Beta2 microglobulinuria has proved particularly useful in identifying cases and has been proposed and used as a marker of the disease.
2. A significant fraction of the protein is low molecular weight (eg, immunoglobulin light chains, beta2 microglobulin, lysozyme, peptide hormones). These proteins are normally taken up by the proximal tubules and broken down there. Thus, in diseases predominantly involving tubular structures, decreased endocytosis of filtered proteins leads to the characteristic tubular proteinuria.
3. Clinical investigations in hepatic glomerulopathy can show modest or significant elevation in serum creatinine, in renal failure evidence of tubular dysfunction.Proteinuria is usually moderate, often more than 1 g/d. Quantitative determination of urine protein may also be important. The main fraction of the protein in urine is high molecular weight**.**A microscopic analysis of urine sediment may reveal casts, WBCs, eosinophils, and crystals.
4. Ultrasonography is noninvasive imaging technique that is extremely helpful in identifying renal implication in liver diseases. A combination of ultrasonography and flat plate kidney, ureter, and bladder radiography is helpful in the identification of kidney abnomalities.In many instances, similar information can be obtained by ultrasonography without exposing the patient to potentially nephrotoxic contrast.
5. Computed tomography (CT) scanning provides information similar to ultrasonographic scanning in the workup of kidney disease, generally with greater resolution.
6. Kidney biopsy is the definitive test for diagnosing of hepatic glomerulonephritis or interstitial nephritis, particularly in cases in which the clinical diagnosis is difficult. Because the differential diagnosis of acute tubulointerstitial nephritis encompasses multiple etiologies, consider kidney biopsy when the diagnosis is not obvious.
7. Although the clinical presentation is often sufficient to make the diagnosis, renal biopsy is required to make a definitive diagnosis.Kidney biopsy shows mononuclear and often eosinophilic cellular infiltration of the renal parenchyma with sparing of the glomeruli (nephropathy).Sometimes, interstitial changes such as fibrosis and atrophy are also present.

Tests of evaluation

1. A well recognized glomerulopathy associated with chronic HBV infection is

a) membranous glomerulonephritis
b) membranoproliferative glomerulonephritis
c) focal and segmental glomerular sclerosis

2. The treatment of HBV-related glomerular diseases has to be focused onthe following objectives, exept:

a) liver function normalization
b) prevention of hbv-related hepatic complications
c) permanent eradication of Helicobacter Pilory
d) treatment of nephrotic syndrome
e) bacterial infection

3.Therapeutic options in patients with HBC -related glomerulonephritis includes:

a) interferon - IFN-α
b) lamivudine
c) adefovir dipivoxil,
d) steroids and cytotoxic agents

4. This findings are more common of hepatic tubulointerstitial nephrites, exept:

a) a lack of significant proteinuria and hypoalbuminemia;
b) the presence of sterile pyuria and white blood cell
c) hematuria and red blood cell casts;
d) the presence of a concentrated urine
e) polyuria and nocturia.

5. Biological hepatic cytolysis syndrome include:

a) increase in ALAT
b) hypoalbuminemia
c) the decrease in ASAT
d) hypergammaglobulinemia
e) increase in 5'-nucleotidase

6. In what circumstances increase the range of glutamyltranspeptidase?

a) gastroduodenal ulcer
b) chronic pancreatitis
c) chronic cholecystitis
d) alcoholic liver disease
e) gluten enteropathy

7. What are the signs that can not be found in acute alcoholic hepatitis?

a) decreased in serum vIGA

b) increased GGTP

c) increase in transaminases

d) thrombocytopenia

e) leukocytosis

8. Which of the hepatitis viruses have DNA nucleic acid?

a) Hepatitis A

b) Hepatitis B

c) Hepatitis C

d) Hepatitis D

e) All

9. In type 1 HRS precipitating factor are, exept:

a) bacterial infections

b) large-volume paracentesis without albumin infusion,

c) gastrointestinal bleeding

d) acute alcoholic hepatitis

e) cirrhotic cardiomyopathy

10. HCV infection can be a "trigger mechanism" in development of:

a) autoimmune Hepatitis

b) sclerosing cholangitis

c) primary biliary cirrhosis

d) HDV Infection

e) HBV Infection

11. The evolution of chronic hepatitis B is caused by:

a) immunological tolerance

b) reaction of the immune system

c) primary or secondary immunodeficiency

d) all listed

12. What is the only element that distinguishes chronic active hepatitis certainty from persistent?

a) trend in 6 months

b) elevated transaminases above 5 times normal values

c) accelerated ESR

d) histological appearance

e) significant hypergammaglobulinemia

13. What is the necessary criteria for the diagnosis of chronic active hepatitis?

a) Jaundice
b) ALT> 5% of normal
c) hypoalbuminemia
d) biopsy type of necrotic lesions
e) anamnestic viral hepatitis

14. After what minimum interval of development we have chronic hepatitis?

a) 3 months
b) 5 months
c) 6 months
d) 9 months
e) 12 months

15. The presence of antimitochondrial antibody is specific for:

a) Acute Hepatitis A
b) primary biliary cirrhosis
c) alcoholic cirrhosis
d) Disease Wilson - Conovalov
e) Acute Hepatitis B

16. Early symptom in primary biliary cirrhosis is

a) Jaundice
b) Itching
c) Fever
d) right upper quadrant pain
e) Ascites

17. Name the syndrome on which we can assume evolution to hepatic cirrhosis:

a) astheno-vegetative syndrome
b) cytolytic syndrome
c) immune-inflammatory syndrome
d) portal hypertension syndrome

18. What are the histological signs you can meet in an active cirrhosis?

a) The presence of lymphocytic inflammatory infiltrate in cell
b) cell necrosis
c) The presence of diffuse fibrotic tissue
d) regenerative nodules

19. Name the syndrome that characterizes the stage of decompensation in liver cirrhosis:

a) Syndrome of hypersplenism
b) immune-inflammatory syndrome
c) hepatic insufficiency syndrome
d) astheno-neurotic syndrome
e) cholestatic syndrome

20. Upper gastrointestinal bleeding in cirrhosis occurs more frequently in one of the following mechanisms:

a) rupture of esophageal varices
b) Mallory-Weiss syndrome
c) hepato-renal syndrom
d) Erosion in oesophageal reflux
e) Haemorrhagic gastritis

21. Hepatic encephalopathy in liver cirrhosis can be triggered by the following factors, except:

a) hiperproteic diet
b) hyperglucidic diet
c)Hypokalemia
d) bleeding from esophageal varices
e) sedative treatment

22. Hypoalbuminemia in liver cirrhosis glomerulophathy is attributable to:

a) high catabolism
b) impairment of hepatic synthesis
c) exudative gastroenteropathy
d) malabsorption syndrome
e) proteinuria

23. Which of the clinical manifestations are not specific for liver cancer?

a) ascites
b) hepatomegaly
c) pain in the right upper quadrant
d) jaundice

24. What are the marker of liver cancer:

a) erythrocytosis
b) thrombocytosis
c) α-fetoprotein
d) hypercalcemia
e) carbonic anhydrase

25. What is the importance of installing jaundice during glomerular hepatitis?

a) Haemolysis increased by increasing serum pancreatic enzymes

b) Development of a pancreatic head cancer

c) hepato-cellular failure

26. The clinical presentation of liver cirrhosis include signs, except:

a) biliary pain

b) Jaundice

c) Fever

d) Heartburn

e) Hepatomegaly

27. In which of the following conditions may occur haematemesis?

a) catarrhal oesophagitis

b) gastric varices

c) Stress Ulcers

d) Zollinger-Ellison Syndrome

e) Disease Mallory-Weis

28. Name the possible complications of decompensated liver cirrhosis.

a) Barrett's syndrome

b) esophageal ulcer

c) pyloric stenosis

d) upper gastrointestinal bleeding

e) esophageal cancer

29. Pathogenetic treatment of hepatic glomerulophathy include:

a) Antiviral treatment of hepatites

b) antisecretory medication(proton pump inhibitors (PPIs) or H2 receptor blockers)

c) NSAIDs

d) Prokinetics

Answers to the testes

1. a
2. e
3. a, b, c
4. d
5. a, d, e
6. d
7. e
8. b
9. e
10. a
11. c
12. d
13. d
14. c
15. b
16. b
17. d
18. d
19. c
20. a, c
21. b

22. b

23. d

24. c

25. c

26. a

27. e

28. d

29.a

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