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WJN covers topics concerning kidney development, renal regeneration, kidney tumors, therapy of renal disease, hemodialysis, peritoneal dialysis, kidney transplantation, diagnostic imaging, evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of nephrology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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EDITORIAL

Changing picture of renal cortical necrosis in acute kidney injury in developing country

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Abstract

Renal cortical necrosis (RCN) is characterized by patchy or diffuse ischemic destruction of all the elements of renal cortex resulting from significantly diminished renal arterial perfusion due to vascular spasm and microvascular injury. In addition, direct endothelial injury particularly in setting of sepsis, eclampsia, haemolytic uremic syndrome (HUS) and snake bite may lead to endovascular thrombosis with subsequent renal ischemia. Progression to end stage renal disease is a rule in diffuse cortical necrosis. It is a rare cause of acute kidney injury (AKI) in developed countries with frequency of 1.9%-2% of all patients with AKI. In contrast, RCN incidence is higher in developing countries ranging between 6%-7% of all causes of AKI. Obstetric complications (septic abortion, puerperal sepsis, abruptio placentae, postpartum haemorrhage and eclampsia) are the main (60%-70%) causes of RCN in developing countries. The remaining 30%-40% cases of RCN are caused by non-obstetrical causes, mostly due to sepsis and HUS. The incidence of RCN ranges from 10% to 30% of all cases of obstetric AKI compared with only 5% in non-gravid patients. In the developed countries, RCN accounts for 2% of all cases of AKI in adults and more than 20% of AKI during the third trimester of pregnancy. The reported incidence of RCN in obstetrical AKI varies between 18%-42.8% in different Indian studies. However, the overall incidence of RCN in pregnancy related AKI has decreased from 20%-30% to 5% in the past two decades in India. Currently RCN accounts for 3% of all causes of AKI. The incidence of RCN in obstetrical AKI was 1.44% in our recent study. HUS is most common cause of RCN in non-obstetrical group, while puerperal sepsis is leading cause of RCN in obstetric group. Because of the catastrophic sequelae of RCN, its prevention and aggressive management should always be important for the better renal outcome and prognosis of the patients.

Key words: Acute kidney injury; Hemolytic uremic syndrome; Renal cortical necrosis; Postpartum hemorrhage; Septic abortion; Puerperal sepsis; Eclampsia

Core tip: Acute kidney injury (AKI) due to renal cortical necrosis (RCN) is rare in developed countries with reported incidence of less than 2% of all cases of acute renal failure. In contrast, its incidence is higher in developing countries ranging between 6%-7% of all causes of acute renal failure (ARF). Pregnancy related complications are the most common cause of RCN. With improved health care, wider availability of dialysis, and marked decline in septic abortion, the incidence and severity of RCN has decreased in developing countries in recent years. RCN accounts for 3% of all causes of AKI in our recent study. The current incidence of RCN in obstetrical AKI was 1.44% in 2003-2014. The most common cause of RCN is haemolytic uremic syndrome among non-obstetric patients and puerperal sepsis is the leading cause of RCN in pregnant patients. The strategy involving prevention and effective management of haemorrhagic and septic complications of pregnancy will further reduce the RCN incidence in pregnant patients in developing countries.

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INTRODUCTION

Renal cortical necrosis (RCN) is a potentially fatal variety of kidney disease with adverse and serious outcomes. The total ischemic necrosis of allthe element (glomeruli, blood vessel and tubule) of the affected area of renal cortex is a typical histological feature of RCN. RCN is irreversible lesion leading to total loss of kidney function and end stage kidney failure in complete variety of cortical necrosis. However, recovery of renal function is variable in the incomplete type of cortical necrosis depending upon the amount of necrosed nephron in the kidney. RCN result from severe degree of renal ischemia secondary to significantly reduced renal tissue perfusion usually on account of intravascular coagulation, microvascular injury or extreme vascular spasm. The following two types of cortical necrosis have been identified on the basis of renal histology: (1) diffuse cortical necrosis: Confluent global cortical destruction extends into the columns of bertin. Thin rim of subcapsular and Juxtamedullary tissue is preserved. Irreversible renal failure leading to end stage renal diseases (ESRD) is the final outcome of diffuse cortical necrosis; and (2) patchy cortical necrosis: Contiguous area of cortical necrosis involve up to one-third to half of the entire cortical tissue. Partial recovery of renal function is known to occur in patchy cortical necrosis.

Renal histology of 113 patients with acute renal cortical necrosis (ACN) revealed complete and patchy cortical necrosis in 62.8% and 37.2% patients, respectively[1]. In our series of 57 patient with RCN, diffuse cortical necrosis was observed in 41 (72%) cases while, patchy cortical necrosis was noted in 16 (28%) patients[2]. Complete and patchy cortical necroses were reported in 80% and 20% of cases from another Indian study[3]. Diffuse and patchy cortical necrosis were noted in 84.2% and 15.8% of patient respectively from our centre earlier[4].

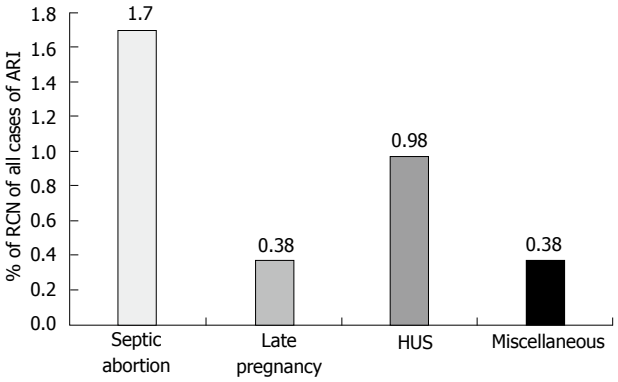

Figure 1 Causes of renal cortical necrosis of all cases of acute renal failure (*n* = 1822); 1984-2005. Adapted from Prakash *et al*[2]. HUS: Hemolytic uremic syndrome; RCN: Renal cortical necrosis.

EPIDEMIOLOGY OF RCN

RCN account for less than 2% of all cases of acute renal failure (ARF) in developed country and is rarely reported[5-7]. In contrast to developed country, the incidence of RCN is higher in developing country ranged between 6%-7% of all causes of acute kidney injury (AKI)[4,8-9]. In our previous study the incidence of RCN was 6.3% in patients with AKI[4]. Another Indian study from Chandigarh observed RCN in 7.1% of patients dialyzed for ARF[3,9]. However, decreased incidence of septic abortion related obstetric AKI resulted in reduced incidence of RCN in Indian patients in recent years[2]. To other previous study from India also reported a declining trend (3.8%-4.6%) in the incidence of RCN in patients with AKI similar to our study[1,2,10]. In a series of 1822 patients with ARF, RCN was observed in 57 (3.12%) patients in our most recent study[2]. The overall incidence of RCN decreased to 1.6% (of total cases of acute renal failure) in 1995-2005 from 6.7% in 1984-1994[2]. Septic abortion in obstetric group and haemolytic uremic syndrome (HUS) in non-obstetric group contributed to RCN in 1.7% and 0.98% of cases respectively, of total ARF cases (Figure 1). RCN was reported in one case (0.13%) of 46 patients undergoing kidney biopsy in a series of 748 cases of acute renal failure[11]. Thus, in contrast to developed world (Europe and North America) the incidence of RCN is still high in developing country. The septic complication of pregnancy such as puerperal sepsis and septic abortion is a major cause of higher incidence of RCN in developing countries including

India[1,2,4]. The causes of RCN are divided in two group: (1) obstetrical; and (2) non-obstetrical causes. Pregnancy related complications are the most common (50%-70%) causes of RCN and 20%-30% of total cases of RCN are due to non-obstetrical condition. RCN of non-obstetrical origin have higher incidence in male than female[4,6,12]. The various non-obstetrical causes of RCN include; extensive burns, sepsis, HUS, pancreatitis, snake bite, and diabetic ketoacidosis[1,3,13].

RCN of obstetric origin

Septic abortion, abruptio placentae, puerperal sepsis, eclampsia, obstetric haemorrhage, intrauterine death, and thrombotic microangiopathy of pregnancy (P-TMA) are the causes of RCN in a pregnant women[5,14-17]. Overall, obstetrical causes are the dominant causes of RCN account for 56%-61% of cases[1,2,18,19]. The RCN is reported to occur in 10%-30% of all cases of pregnancy related AKI compared with approximately in 5% of non-pregnant women[20]. We reported RCN in 25% of obstetric ARF in our previous study[19]. Of 57 patients with RCN; pregnancy-associated complication and non-pregnant condition were causative factor for RCN in 32 (52.2%) and 25 (43.8%) respectively[2]. We reported RCN due to pregnancy related complications in 15.2% of obstetric ARF; with higher (11.9%) incidence in post-abortal AKI compare to lower (3.3%) incidence in late pregnancy-AKI[2]. The incidence of RCN was 9% among patient with obstetric AKI in a study from Pakistan[21]. The RCN incidence has decreased from 17% in 1982-1991 to 2.4% in 1992-2002 in obstetric ARF in our recent publication[15]. Thus, the overall incidence of RCN in pregnancy associated AKI has decreased from 20%-30% to 5% in the last two decades in developing countries[2]. The current (2003-2014) incidence of RCN is 1.44% (1/69) in obstetric AKI in our study[22]. Post-abortal sepsis is a common cause of RCN in obstetric AKI in developing countries while, abruptio placentae is responsible for RCN in 50%-60% of case in pregnancy in developed countries[13,23]. Thus, septic abortion is common cause of RCN in developing countries but rarely reported from developed world[14,16,24]. The abortion is commonly conducted by unskilled persons mostly under unhygienic condition which leads to higher incidence of post-abortal sepsis. This possibly may explain higher incidence of RCN in post-abortal AKI in developing world. It is postulated that endothelial injury due to endotoxin may cause endovascular damage and vascular thrombosis with consequent renal ischemia in patient with sepsis and septic abortion.

RCN of non-obstetric origin

The various non-obstetrical causes of RCN include; extensive burns, snake bite, sepsis, pancreatitis, HUS, infancy and childhood dehydration, malaria and drugs and toxin[1,2,25-29]. Non-pregnancy associated complication accounted for RCN in 34.8% of total ARF cases in our earlier study[16]. RCN was due to pregnancy and non-pregnancy related complications, in 56.2% and 43.8% cases respectively in our recent publication[2]. HUS was the most common cause 18/25 (72%) of cortical necrosis in the non-obstetrical group[2]. Severe sepsis, extensive burns (80%), massive gastrointestinal haemorrhage, acute pancreatitis and diarrhoea associated shock are other causes of RCN in non-pregnant group[2]. The changing clinical feature of RCN was analysed and compared in 28 patients in English literature before and after 1980 from two countries; France (F) and India (I). This analysis revealed that pregnancy related cortical necrosis decrease to 28% after 1980 from 68% (F) and 71% (I) before 1980, while non-pregnancy related cortical necrosis increased to 72% after 1980 from 32% (F) and 29 (I) before 1980. The RCN was due to sepsis in 4/12 (F) and snake bite 6/14 (I) cases before 1980 but drug associated cortical necrosis was observed in 4/21 patient after1980 among the non-obstetrical causes of cortical necrosis[30]. RCN was reported in 19.9% of patient among 131 cases with post-surgical ARF from Japan in an autopsy study[31]. Despite a bit increasing trends in non-obstetrical cause of RCN, obstetrical complication is still remains the dominant cause of RCN in developing country. The development of RCN in live kidney donor and malaria was noted in Indian literature[32,33]. Figure 2 shows the RCN in live kidney donor. Donor was on maintenance haemodialysis for 4 mo and she eventually died of severe sepsis related to pneumonia[33]. RCN developed in a congenital solitary kidney following Road Traffic accident (Figure 3) in a child aged 11 years.

PATHOGENETIC MECHANISMS OF RCN

The pathophysiological events leading to RCN are poorly understood. However, significantly diminished renal arterial perfusion is the final common pathway resulting in ischemic necrosis of renal cortex. The exact pathogenetic mechanism of RCN is not completely known. The vasospasm of small vessel and liberation of toxin with consequent endothelial injury seems to be initiating event in the process of cortical necrosis[34,35]. The vasculature in pregnancy is more sensitive to vasoconstrictors, possibly related to sex hormone[35]. ACN and the generalised Schwartzmann reaction induced by endotoxin in rabbit have similar clinical feature[36-38]. Two small doses of endotoxin given at interval of 24 h may cause generalised Schwartzmann reaction in non-pregnant animal while only one dose is sufficient to produce this phenomenon in pregnant rabbits[37]. Intravascular coagulation was considered as the initial event in pathogenesis of RCN. However, available evidences does not support the role of intravascular coagulation in the genesis of RCN[6].

The role of endothelium-derived vasoactive substance particularly endothelin-1 has been suggested in the pathogenesis of ischemic ARF. The endothelin-1 is one of the most potent vasoconstrictor substance known[39], and renal vasculature appears to be 10 times more sensitive to this effect of endothelin-1 compared

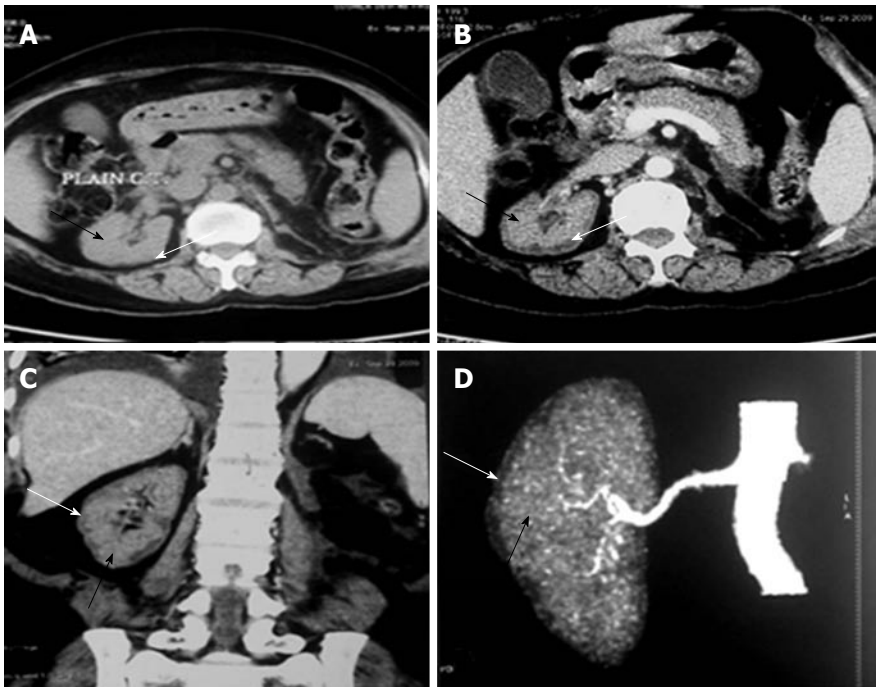

Figure 2 Renal cortical necrosis in a living kidney donor. Adapted from Prakash *et al*[32]. Non-contrast (A) computed tomography (CT) scan of abdomen at the level of right hilum showing hypoattenuating peripheral cortical rim (white arrow) as compared to the inner isoattenuating parenchyma (black arrow), On contrast-enhanced axial (B) and coronal (C) scans the central viable parenchyma enhances (black arrow) while the peripheral necrosed cortex does not show any significant enhancement (white arrow). Overall picture is suggesting renal cortical necrosis. The corresponding appearance is also well noted CT Angiogram (D) showing absent uniform nephrogram (white arrow).

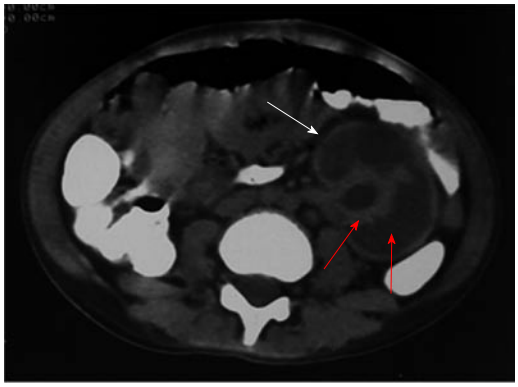

Figure 3 Contrast enhanced computed tomography showing diffuse cortical necrosis in solitary left kidney after road traffic accident in a child aged 11 years. This image shows isoattenuated peripheral cortical rim (white arrow) and hypoattenuated parenchyma (red arrow).

to all other vascular organ[40]. It is suggested that endotoxin initiate endothelial injury with subsequent development of intravascular thrombosis and reduce renal perfusion causing cortical necrosis in patient with sepsis. The endothelial injury seems to be a primary event in development of TMA[41]. In patient with HELLP syndrome, endothelial damage may progress to endovascular thrombosis leading to lumen occlusion, hypoperfusion and ischemic necrosis of renal cortex[42]. Two possible pathogenetic factors may contribute the development of RCN: (1) renal hypo-perfusion resulting from blood loss or hypotension such as in postpartum haemorrhage; and (2) vascular endothelial injury either through direct mechanism (HUS, eclampsia and snake bite) or indirect mechanism *via* release of circulating substances (sepsis, pancreatitis and intravascular haemolysis). It is postulated that endothelin may act as final common factor leading to renal damage and subsequent RCN, because both renal hypo-perfusion and endothelial injury stimulate release of endothelin from vascular endothelial cell. However, further detailed studies are required to established the possible role of endothelin in the pathogenesis of RCN.

CLINICAL AND DIAGNOSTIC FEATURES OF RCN

RCN is a rare but catastrophic cause of AKI. Absolute anuria (urine output nil in 24 h) or anuria (urine output < 100 mL/24 h) are the usual presenting symptoms of acute RCN. Because of the systemic nature of illness causing RCN, the lesion is usually bilateral. Prolonged anuria (> 4 wk) in clinical setting of haemorrhage, sepsis, shock or disseminated intravascular coagulation suggests the clinical diagnosis of RCN. The mean duration of absolute anuria from the onset till death or partial recovery of renal function while on dialysis was 24.5 ± 26.2 (range 6-100) d in our study[2,4]. Hematuria (microscopic or gross) can be seen in patients with ACN. The renal biopsy is the gold standard to confirm the diagnosis of RCN. The typical histological feature of RCN is ischemic necrosis of all elements of renal parenchyma of cortical region (Figure 4). RCN was diagnosed on

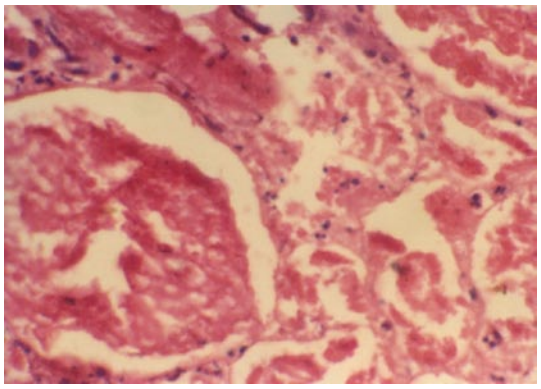

Figure 4 Glomeruli and neighbouring tubules are showing coagulative necrosis. There is complete loss of nuclei in glomeruli and tubules, but connective tissue framework is preserved. Neutrophilic infiltrations are seen around necrosed glomeruli and in interstitium (HE × 250). Typical histologic feature of renal cortical necrosis.

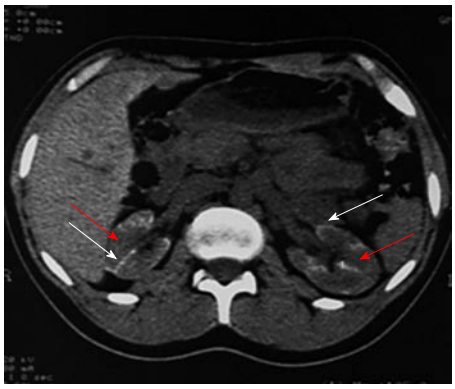

Figure 5 Non contrast computed tomography showing bilateral cortical calcification in a patient with renal cortical necrosis 72 d after acute pancreatitis. Non contrast computed tomography scan of abdomen at the level of renal hila showing linear hyperattenuation along the renal cortical rim (white arrow) with hypoattenuating medulla (red arrow) in bilateral kidney.

kidney biopsy specimen within the first week of the onset of disease. However, contrast enhanced computed tomography (CECT) scan is a suitable non-invasive modality for the early diagnosis of RCN[43]. The presence of hypoattenuated subcapsular rim of renal cortex on CECT scan is atypical radiological abnormalities in patient with RCN (Figure 3). In addition, a non-contrast CT scan (NCCT) is more sensitive in picking up cortical calcification. However, renal cortical calcification develop too late and also not observed in all patients with RCN[20,44,45] (Figure 5). Thus, demonstration of cortical calcification on NCCT scan is not useful in early diagnosis of RCN. Other less invasive method of diagnosis like MRI scan are useful alternative[46]. Recently, contrast enhanced ultrasound scan is found to another non-invasive modality for early diagnosis of RCN[47].

CLINICAL COURSE AND OUTCOMES OF RCN

The clinical course of patients with RCN can be divided into five broad groups: (1) death in uraemia during the acute phase; (2) survival without dialysis; (3) late return to dialysis/transplant; (4) survival only with chronic maintenance dialysis/transplant; and (5) late resumption of sufficient renal function to become dialysis independent. The mortality was 87% during acute phase of illness in our previous study[4]. However, mortality decreased to 19% in 1995-2005 from 72% in 1984-1994[2]. The maternal mortality in obstetric RCN was 72.7% in 1982-1991. Mortality was observed in 1 of 3 patients in 1992-2002 and no mortality in the last decades. Thus, maternal mortality reduced to zero in 2003-2014 from 72.7% in 1982-1991[22]. The causes of death during acute phase of illness are; severe uraemia, sepsis, pulmonary oedema, gastrointestinal haemorrhage and hyperkalemia including multiorgan failure[2]. Thus, the majority of deaths are due to sepsis and uremic complication in those who could not afford dialysis. However, the prognosis and survival of patients with RCN has improved markedly in our recent publication due to availability of renal replacement therapy and overall improved medical care[2,15,22]. Survival without dialysis is possible in patients with patchy cortical necrosis because surviving nephrons carry the function of the remaining kidney. In certain patients, there may be slow rise in creatinine clearance and a gradual gain in renal function over one to two years, so that the glomerular filtration rate may reach a final plateau level of approximately 20-24 mL/min[48,49]. It is assumed that juxtamedullary glomeruli (which comprise 15%-20% of total) escape destruction, even in the complete cortical necrosis and that early functional return is due to recovery of these nephron segment. The deterioration in renal function had been reported several years (1-10 years) after the acute cortical necrosis in a significant number of patients. Factors causing these late functional downturn are not clear but may include pyelonephritis, hypertension and shrinkage of the kidney due to progressive fibrosis and/or calcification[50,51].

The fate and outcome of RCN has changed in developing countries mainly due to decreasing incidence of RCN in patients with acute renal failure. We observed the incidence of RCN decreased to 1.6% in 1995-2005 from 6.7% in 1984-1994[2]. The incidence of RCN in obstetric AKI has decreased to 2.4% in 1992-2002 from 17% in 1982-1991 in our previous publication[15]. The most recent incidence of RCN in obstetric AKI was 1.44% in our study[22]. This changing picture of RCN is mainly due to a decrease in incidence of poost-abortal sepsis. Public awareness, legalization of abortion law, and overall improved health services are other reasons for such improvement in the prognosis and outcome of cortical necrosis at our centre.

CONCLUSION

The renal prognosis of RCN has improved. The partial recovery of renal function had increased to

33.3% in 1995-2005 from 11% in 1984-1994. The mortality of patients with RCN had markedly reduced to 19% in 1995-2005 from higher mortality of 72% in 1984-1994 due to wider availability of dialysis and overall improvement in health care facilities. Because of decreased mortality, higher (47.6%) proportion of patients with cortical necrosis had progressed to ESRD in 1995-2005, compared to lower (16.6%) number of patients in 1984-1994. Thus, both increased number of patient survival and better renal outcome contributed to improved prognosis of RCN in recent years. In addition to improved prognosis of RCN, overall incidence of RCN has decreased to 3% of total cases of ARF. The current incidence of RCN in obstetric AKI is 1.44% at our centre.

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EDITORIAL

Biomarkers in kidney transplantation: From bench to bedside

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Abstract

Immunosuppressive drug level monitoring and serum creatinine are widely used for kidney transplantation (KT) monitoring. Monitoring of drug level is not the direct measurement of the immune response while the rising of creatinine is too late for detection of allograft injury. Kidney biopsy, the gold standard for KT monitoring, is invasive and may lead to complications. Many biomarkers have been discovered for direct monitoring of the immune system in KT and the benefit of some biomarkers has reached clinical level. In order to use biomarkers for KT monitoring, physicians have to understand the biology including kinetics of each marker. This can guide biomarker selection for specific condition. Herein, we summarize the recent findings of donor specific anti-human leukocyte antigen antibody, B lymphocyte stimulator, interferon-gamma induced protein of 10 kDa, and intracellular adenosine triphosphate monitoring, all of which have very strong evidence support for the clinical use in KT.

Key words: Kidney; Transplantation; Biomarkers; Donor specific antibody; B-cell; B lymphocyte stimulator; Interferon induced protein of 10 kDa; Intracellular adenosine triphosphate

Core tip: There are many studies about roles and benefits of biomarkers in nephrology, including transplantation. Only some of them reach the clinical level with strong evidence support. Biomarkers can guide immunosuppressive adjustment, provide prognostic value, and guide early detect of allograft injury, particularly from allograft rejection. We summarized the potential biomarkers for kidney transplantation monitoring, including clinical implication, strength and weakness of each of them.

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INTRODUCTION

Kidney transplantation (KT) has been succeeded for a long-time but the improvement in graft outcome is only limited in the short-term[1,2]. The keys to achieving long-term kidney allograft survival are early detection of treatable cause of allograft dysfunction and the appropriate tailoring of immunosuppression. Over immunosuppression can result in infections and cancers whereas under immunosuppression can cause rejection of the transplanted kidney. Immunosuppressive drug level monitoring is currently the only method broadly used in clinical practice. The gold standard for KT monitoring is biopsy which is invasive. However, kidney biopsy is only useful once rejection has already occurred. The procedure is unable to predict rejection. Recently, there are growing numbers of biomarker studies for KT, ranged from experimental to clinical level. Understanding immunologic and physiologic changes of allograft and directly monitoring through blood and urine testing can guide management and immunosuppressive adjustment.

There are two main objectives for biomarker testing: (1) for diagnosis; and (2) for prognostic and outcome prediction. Some biomarkers can guide diagnosis and management during allograft dysfunction, whereas others can predict outcome and guide long-term management including immunosuppressive adjustment for rejection and drug toxicity prevention. The samples mainly used for monitoring are blood and urine. Blood sample is easily taken and handled but it is not directly excreted from the kidney allograft and can be diluted in the blood stream. Urine sample is directly contacted and excreted from the allograft which more represents kidney environment than blood sample. However, urine sample can be interfered by urine pH, urine protein, and urine volume. Furthermore, urine sample is not easily collected during anuric phase. Herein, we summarized the recent findings in blood and urine biomarkers mainly focusing on methods which can be easily tested in clinical practice of KT.

DONOR SPECIFIC ANTIBODY

Donor specific antibody (DSA) is the anti-human leukocyte antigen (HLA) which is specific to donor HLA. It is the major obstacle in KT. In the study of 1329 KT recipients, the 4-year allograft survival was lower in recipients with positive DSA detected compared with the recipients with negative DSA[3]. There are many methods for DSA detection, ranged from lymphocytotoxic anti-human globulin (LCT-AHG) which has least sensitivity to the most sensitive and specific assay, the solid phase single antigen bead (SAB). DSA is a major cause of antibody mediated rejection (ABMR). Positive DSA by LCT-AHG is the absolute contraindication for KT. However, positive SAB but negative LCT-AHG (SAB positive/LCT-AHG negative) is not the absolute contraindication for KT. DSA is now the most widely used test in KT. DSA can be monitored from pre-transplantation period till many years post-transplantation. The pre-transplant DSA can predict post-transplant outcomes and guide perioperative management[4,5]. In post-transplantation period, DSA is included in one of the criteria for ABMR[6]. The newly presence of DSA (*de novo* DSA) prompts physician for evaluation for ABMR and increasing the level of immunosuppression before allograft function deteriorates (Figure 1)[7]. However, there are certain issues to be concerned in DSA interpretation. Only substantial number of the patients who developed de novo DSA have allograft function deterioration. A cohort study by Wu *et al*[8] showed that 9.5% and 19.0% of *de novo* DSA patients developed early allograft failure and early allograft function deterioration, respectively during a 3-year follow up. Indeed, the graft function of the 70% of *de novo* DSA patients remains stable for years. As such, DSA can be classified into the pathogenic- and non-pathogenic-DSA. The pathogenic DSA is likely to have at least one of these features: (1) DSA to HLA-DQ; (2) mean fluorescence intensity (MFI) > 7000; (3) DSA with C1q activating capacity; and (4) IgG1 or IgG3 subclasses[9]. The presence of DSA together with one of these characteristics prompts physician for allograft biopsy and treatment of ABMR to remove this pathogenic DSA in those who have pathological clues of allograft injury.

B LYMPHOCYTE STIMULATOR

As anti-HLA antibody is the major barrier in KT, plasma cell and B-cell are currently the major targets of treatment. B lymphocyte stimulator (BLyS) is produced mainly by innate immune cells and binds to its receptor on B-cell and plasma cell. There are two cytokines in the BLyS system, B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL). BLyS is required for the development of B-cell in earlier stages whereas APRIL is required for plasma cell survival[10]. In a model of murine cardiac allograft, BAFF deficient mice had longer allograft survival when compared to wild-type[11].

In pre-transplantation period, BAFF is correlated with the degree of sensitization. A higher BAFF level was associated with a higher MFI of pre-transplant anti-HLA antibody[12]. Elevated pre-transplant serum BAFF level was also associated with an increased risk of the subsequent ABMR[13]. Patients with high post-transplant soluble BAFF levels had a significantly higher risk of developing de novo DSA[14].

There are some issues to be concerned in interpretation of BLyS in KT. The first is the balancing between BLyS production by innate immune cells and utilization by B-cell. Increments in BLyS levels may be due to

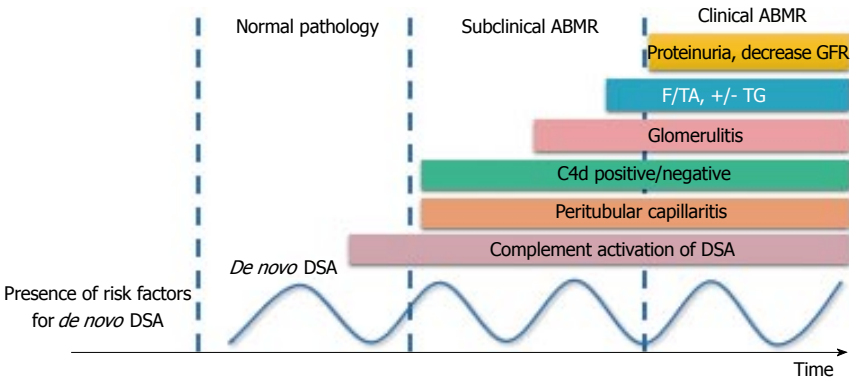

Figure 1 Graft injury and clinical presentation after development of *de novo* donor specific antibody. The pathologic injury of ABMR starts from microvascular inflammation, including peritubular capillaritis, C4d staining in allograft, and glomerulitis, to interstitial fibrosis/tubular atrophy (IF/TA) and transplant glomerulopathy (TG). GFR: Glomerular filtration rate; ABMR: Antibody mediated rejection; DSA: Donor specific antibody.

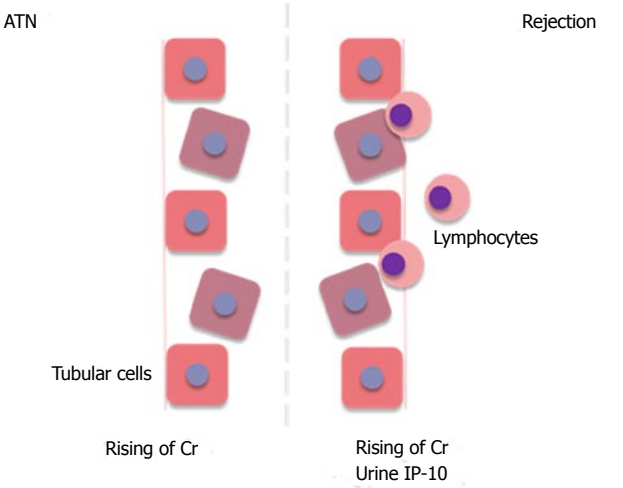

Figure 2 Comparing the mechanism of acute tubular necrosis and rejection. The rejection causes tubular damage similar to ATN but lymphocytes infiltration can leads to elevation of urinary IP-10 in rejection. ATN: Acute tubular necrosis; Cr: Creatinine; IP-10: Interferon-gamma induced protein of 10 kDa.

either increased production and/or reduced B-cell consumption. Recipients who received anti-rejection therapy with rituximab, a potent B-cell inhibitor, had a significant peak of BLyS levels at 3 mo post-treatment which can be explained by lower BLyS consumption from B-cells inhibition[15]. Second, there is a number of evidence in the roles of BLyS in immune regulation. BLyS is not only needed in B-cell or plasma cell activation, but also required by the regulatory B-cell which plays a very important role in immune regulation and transplantation tolerance[16]. Transplantation tolerance is a condition that the recipient immune system accepts allograft as a part of recipient and is the holy grail of transplantation. Recipients with tolerance require less immunosuppression or no immunosuppression needed in some circumstances. Increasing BLyS level in some certain conditions may be favorable as it may be a potential induction of transplantation tolerance.

We recently studied the benefit of BAFF testing in both low risk and high risk newly KT recipients and found that among recipient with positive pre-transplant DSA, the 6-month ABMR rate in recipients with higher perioperative serum BAFF level was significantly higher than those with lower perioperative BAFF level. In recipients with negative DSA, none of the patients with lower BAFF level developed ABMR while 17% of the higher BAFF recipients, despite negative DSA, still experienced ABMR (manuscript in preparation). This finding supports the benefit of adding BAFF in to pre-transplant immunologic risk evaluation together with DSA testing.

INTERFERON-GAMMA INDUCED PROTEIN OF 10 KDA

Induced protein of 10 kDa (IP-10) (also called CXCL-10) is one of the CXCR3 chemokine family. It is produced by tubular cells, mesangial cells and inflammatory cells and can be found in the kidney allograft[17]. In the setting of tubular inflammation, mainly acute rejection, IP-10 is elevated and highly expressed in urine (Figure 2). Recipients with T-cell mediated rejection or ABMR revealed higher urine IP-10 level compared to other pathological findings[18-20]. Many studies found that IP-10 measurement can detect subclinical tubulitis/rejection in surveillance allograft biopsy before allograft dysfunction developed[18,21].

In the setting of delayed graft function (DGF), early acute rejection, which needs early treatment, has to be differentiated from ischemic acute tubular necrosis (ATN). Concerning the higher risk of bleeding complication during this period, the clinician is reluctant to perform kidney biopsy. Our group studied the usefulness of urine IP-10 monitoring during DGF period. Recipients with early post-operative ABMR had significantly higher urine IP-10 compared with recipients with pure ischemic ATN (manuscript in preparation). However, an adequate amount of urine is needed for IP-10 testing.

ADENOSINE TRIPHOSPHATE MEASUREMENT

Since pharmacokinetic monitoring of immunosuppressive drug dose not directly predict T-cell reactivity, measurement of nucleotide adenosine triphosphate (ATP) from T-cell allows direct assessment of immunosuppression. The Food and Drug Administration has approved the ImmuKnow® assay for measuring intracellular ATP of T-cell for immune system monitoring in KT recipients.

The low ATP patients were associated with infections, whereas the high ATP patients were associated with rejection[22]. A randomized controlled trial from Ravaioli *et al*[23] in liver transplant recipients found that dosing of immunosuppression guided by ATP monitoring provided higher 1-year patient survival compared to convention immunosuppressive drug adjustment. However, some studies revealed no association between ATP level and transplantation outcomes[24-26]. This can be explained by the fact that the ATP level is not associated only with the T-cell reactivity but is also affected by the number of white blood cell (WBC), particularly in patients receiving lymphocyte depleting antibody. The number of WBC has to be considered when interpreting the result of ATP values. ATP measurement should not be used solely without other monitorings.

CONCLUSION

There are many biomarkers for KT monitoring. Each biomarker provides specific purpose for measurement. Knowing the immunologic mechanisms can guide biomarker selection. Together with biomarker monitoring, clinical clues should not be overlooked in taking care of KT recipients.

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REVIEW

Medical and alternative therapies in urinary tract stone disease

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Abstract

Nephrolithiasis is a serious problem for both patients and the health system. Recurrence stands out as a significant problem in urinary system stone disease, the prevalence of which is increasing gradually. If recurrence is not prevented, patients may go through recurrent operations due to nephrolithiasis. While classical therapeutic options are available for all stone types, the number of randomized controlled studies and extensive meta-analyses focusing on their efficiency are inadequate. Various alternative therapeutic options to these medical therapies also stand out in recent years. The etiology of urolithiasis is multifactorial and not always related to nutritional factors. Nutrition therapy seems to be useful, either along with pharmacological therapy or as a monotherapy. General nutrition guidelines are useful in promoting public health and developing nutrition plans that reduce the risk or attenuate the effects of diseases affected by nutrition. Nutrition therapy involves the evaluation of a patient's nutritional state and intake, the diagnosis of nutrition risk factors, and the organization and application of a nutrition program. The main target is the reduction or prevention of calculus formation and growth *via* decreasing lithogenic risk factors and increasing lithogenic inhibitors in urine. This review focuses briefly on classical medical therapy, along with alternative options, related diets, and medical expulsive therapy.

Key words: Urolithiasis; Prevention; Stone medical therapy; Nutrition therapy; Diet; Hypercalciuria; Hyperoxaluria; Hyperuricosuria; Hypocitraturia; Cysteine stones

Core tip: Nephrolithiasis is a serious problem for both patients and the health system. Recurrence stands out as a significant problem in urinary system stone disease, the prevalence of which is increasing gradually. While classical therapeutic options are available for all stone types, the number of randomized controlled studies and extensive meta-analyses focusing on their efficiency are inadequate. Various alternative therapeutic options to these medical therapies also stand out in recent years. This review focuses briefly on classical medical therapy,

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INTRODUCTION

Nephrolithiasis is a widespread medical problem, with an increased incidence in the last 20 years[1-4]. Its prevalence is expected to rise in the upcoming decades, as has been the case for obesity, diabetes, and metabolic syndrome[2,3]. Another problem related to nephrolithiasis is recurrence. In patients who do not receive prophylaxis following the first attack, recurrence rates are reported as 10% in the first year, 35% in the next 5 years, and 50% in 10 years[5].

If recurrence is not prevented, patients may go through recurrent operations due to nephrolithiasis which, even if said operations are only minimally invasive, still results in hospitalization. This leads to higher monetary costs and loss of manpower, whereas preventing stone formation is far more economic.

Numerous reports have revealed that urinary stone disease recurrence rates can be reduced *via* the correction of environmental and metabolic factors, as well as by the use of certain drugs and diet treatments[6-9]. In a meta-analysis of randomized trials focusing on the effects of drugs and diet on stone recurrence, the risk was shown to be reduced by 26%[10].

Further investigation into the possible pathogenic effect of Randall's plaques and the role of renal tubular crystal retention as a precursor in calcium oxalate (CaOx) nephrolithiasis may allow for the development of new drugs for the prevention of plaque formation and crystal adhesion to kidney cells. Nevertheless, all future studies should aim to understand the molecular/genetic level and pathophysiological mechanism of nephrolithiasis for the development of a targeted therapy.

PHARMACOTHERAPY

Hypercalciuria

Thiazide diuretics are the main treatment for idiopathic hypercalciuria (IH)-related calcium stones. There have been at least 10 randomized controlled trials (RCTs) focusing on the efficacy of thiazide in the prevention of idiopathic calcium kidney stones recurrence. Of these, seven have reported a decline in recurrence rates in treated patients[11-17].

Potassium supplements should normally be applied alongside thiazide treatment in order to prevent hypokalemia and hypocitraturia secondary to thiazide, as well as any possible subsequent side effects[18]. A reduction in bone mineral intensity and an increase in osteoclasis accompanies IH, with some authors claiming that reducing urinary calcium excretion can improve bone histology[19]. Bisphosphonates are effective in the inhibition of bone resorption, and the lower urinary calcium secretion and higher bone mineral intensity provided *via* bisphosphonate treatment was reported in a few studies[20]. Heller *et al*[21] have reported that alendronate prevented the excretion of urinary calcium, decreased 24-h urine calcium, and adjusted calcium equilibrium in 9 calcium stone patients within a short time period. Since no RCTs have yet been conducted to evaluate the efficacy of bisphosphonates on recurrence, bisphosphonate treatment is not currently recommended.

Hyperoxaluria

Two pharmacological agents that can reduce urinary oxalate are magnesium and pyridoxine.

The effect of magnesium in CaOx stone and non-hypomagnesuria patients is explained by the complexes formed among magnesium and oxalate that can lead to a reduction in CaOx supersaturation and inhibit the development of CaOx crystals. Increased magnesium intake additionally leads to an increase in urinary citrate and pH levels. On the other hand, dietary magnesium can reduce intestinal oxalate absorption in a manner similar to that of dietary calcium[22].

Calcium supplements, such as calcium carbonate and calcium citrate, are another potential therapeutic to magnesium supplements, as the latter are relatively less studied in hyperoxaluria treatment and form complexes with oxalate anions by a similar mechanism.

The logic behind vitamin B_6 use, on the other hand, is that its deficiency may cause oxalate leakage in urine[13]. RCTs on the use of pyridoxine in the prevention of recurrent stone disease are lacking in the literature, yet studies without controls in CaOx stone patients suggest that vitamin B_6 decreases urinary oxalate and stone recurrence[14,15].

The discovery of the relationship of oxalate with bacterial flora in the gastrointestinal system has paved the way for research related to the function of probiotics in the management of repeated CaOx stones. Studies revealed that lacking *Oxalobacter formigenes* colonies, which use oxalate as their solitary source of nutrition, could lead to an increase in the incidence of CaOx stones. In multivariate analyses, stone recurrence risk is reduced by 70% in *O. formigenes* colonized individuals[23]. Batislam *et al*[24] investigated *O. formigenes* levels for the first time in stool samples of cases with hyperoxaluria and recurrent nephrolithiasis by real-time PCR, and eventually found reduced levels of *O. formigenes* in cases with hyperoxaluria and recurrent nephrolithiasis.

An increase in the intestinal colonization of oxalate-producing bacteria decreases oxalate absorption, which in turn causes a reduction in urinary oxalate. Use of *O. formigenes* enteric capsules in primary hyperoxaluric

patients decreases urinary oxalate levels substantially, which shows that oral intake is effective on the enteric metabolism of endogenously-produced oxalate[25]. Prospective trials are required to corroborate the efficacy of probiotics on reducing urinary oxalate levels, as well as the side effects. Although current uncontrolled studies show that use of lactic acid bacteria[26] decreases urinary oxalate levels, these are not prospective double-blind placebo-controlled studies[27].

The function of oxalate-reducing bacteria, such as *O. formigenes* in CaOx stone formation, is currently under investigation. A pilot study has shown that *O. formigenes* reduces blood oxalate levels and urinary oxalate excretion in many IH-related calcium stones cases[26], yet these results could not be reproduced completely in a recent multi-centered study. Furthermore, the results acquired from expending lactic acid bacteria as a probiotic for the reduction of urinary oxalate elimination are inconsistent[28]. Treatments involving increased anion transport activity or the upregulation of intestinal luminal oxalate secretion through the use of oxalate binders are among other potential treatment approaches[29].

As calcium binds diet oxalate in the intestinal lumen, calcium supplements may decrease oxalate absorption[30]. Consumption of 2-4 g cholestyramine with every meal is much more beneficial in binding oxalate, yet brings along such inconveniences as an unpleasant taste in the mouth and vitamin K insufficiency[31]. Although the phosphate binding agent sevelamer hydrochloride is thought to decrease oxalate absorption, the conclusions are discrepant[32,33].

Hyperuricosuria

Dietetic purine limitation should be the initial medicinal approach[34], with alternative approaches required for incompatible patients and actual non-responders.

The main strategy in the treatment of uric acid cases is alkalization of the urine, which is more important than uricosuria reduction[35,36]. Typical starting doses to preserve the urine pH between 6.5-7.46 are 40-60 mEq for potassium citrate (KCit) in divided doses, or 1300 mg 2 × 1/d for sodium bicarbonate[37].

Allopurinol addition should be considered for patients with persistent acidic urine that does not alkalize easily. Hyperuricosuric CaOx nephrolithiasis is traditionally a xanthine oxidase inhibitor that is treated with allopurinol, which decreases endogenous uric acid formation and urinary uric acid excretion. The typical daily dose of allopurinol is 100-300 mg[37].

Recent interesting research on uric acid metabolism suggests that novel therapeutic methods may be developed in the future for hyperuricosuric nephrolithiasis and uric acid nephrolithiasis. More specifically, recent studies have shown that novel xanthine oxidase inhibitor (febuxostat) and the recombinant form of uricase enzyme (rasburicase) had superior serum uric acid-reducing effects compared to allopurinol, and are more successful in reducing the periodicity of gout recurrences[38,39]. These drugs should be considered for potential therapeutic agents of stone disease, although they are not yet tested.

Hypocitraturia

While both potassium citrate (KCit)[40] and potassium-magnesium citrate[19] were demonstrated to remarkably reduce hypocitraturia and recurrent urolithiasis formation in randomized stone case studies, sodium-potassium citrate did not exert any beneficial effect[20]. Although KCit is available commercially in tablet, liquid, and powder forms, investigations are ongoing in terms of developing a drug form of potassium-magnesium citrate[37].

The standard initial dose of KCit is 40-60 mEq daily, in divided doses, until the desired citraturia level is achieved[37]. These patients should be closely followed due to the potential for hyperkalemia, which is a theoretical risk due to the use of potassium-containing preparations and the increased glomerular filtration rate of the patients. In addition, some patients speak of gastrointestinal complaints while using KCit. Due to the high monetary cost and low patient compatibility of KCit therapy, its substitution with a dietary treatment was investigated. Lemon juice is naturally rich in citrate, and while it was concluded that drinking lemonade for 21 d increased urinary citrate levels in an uncontrolled metabolic study[41], 2 other recently carried out controlled-metabolic studies have raised doubts concerning the effect of lemonade in reducing recurrence.

Koff *et al*[42] conducted a randomized comparative study where they compared lemonade and KCit therapy in a group of patients with recurrent stones. While no changes were detected in basic urinary citrate or pH levels following lemonade therapy, a notable increase in urine citrate was reported in cases who received KCit. In accordance with these findings, while the use of lemonade is unsuccessful in increasing urine citrate and pH levels, it provides a prominent advantage over KCit due to the increased urine volume.

Cystine stones

Dilution and alkalization of urine, as well as thiol-binding drug and claw (chelation) combination therapy, constitutes the main guidelines of the cystine stone treatment approach. Combinatory use of these drugs may be more effective compared to individual use, due to the relatively higher pKa (8.5) of cysteine[43].

Patients should wake up at least once every night to drink water, as well as drink additional water to prevent concentration of urine at night. Patients can take 10-20 mEq 3 × 1/d KCit to increase urinary pH if it is < 7. Cystine excretion can be mildly decreased with < 100 mmol/d per sodium and 0.8 g/kg per day/protein restriction diets.

If stone recurrence occurs in spite of appropriate fluid intake and base urinary pH, cystine-linking drugs should be added to the treatment. D-penicillamine and tiopronin are the most widely-used thiol-linking

pills. D-penicillamine and tiopronin therapy has been indicated to be beneficial in the reduction of urolithiasis formation in cases where there was no benefit from hydration and alkaline urine.

The frequently-used thiol group anti-hypertensive captopril is another theoretical pharmacological agent in cystinuria treatment. Nevertheless, it is reported that it was not adequately effective in the solubility of cystine in urine, and that it also gave speculative results in a number of small scale studies regarding its ability to decrease urine cystine levels[43].

Struvite stones

Early diagnosis and eradication is essential for struvite stones, due to their fast growth potential and significant morbidity[44].

Long-term, low dose culture-specific antibiotic treatment is significant in the prevention of post-operative new stone growth and progression. Furthermore, minimizing urease concentration may even provide post-operative eradication of small fragments. Treatment with antibiotics only is not a standard approach[45].

Even in the presence of hydroxyurea, acetohydroxamic acid (AHA) is the most frequently used medical agent. In three randomized double-blind studies where AHA was used, stone growth and formation was decreased[46-48]. AHA and antibiotic suppression regimes can typically be recommended in patients that may not be surgery candidates due to serious side effect profiles, and in which potential significant side effects of AHA can be considered as acceptable risks.

MEDICAL EXPULSIVE THERAPY

Medical expulsive therapy (MET) exerts its effects *via* relaxation of the ureter and augmentation of the hydrostatic physical force proximal to the calculus[30].

In a patient that admits with lumbar pain due to ureteric calculi, the most substantial elements predicting the unpremeditated transition of the calculi are the dimension and localization of the stone. Meta-analysis has given the unpremeditated transition ratio of ureteric calculus as 68% and 47% for < 5 mm and 5-10 mm dimensions, respectively[49]. The most widely-used drugs for premedication of ureteric stones are α-1 adrenergic receptor antagonists and calcium channel blockers (CCB). α-1D receptors are the most widely-localized α-adrenergic receptors in the ureter, and are most densely localized in the distal ureter[50]. α-1 adrenergic receptor antagonists reduce the frequency and strength of the urethral contractions[51]. The CCB nifedipine was demonstrated to soften urethral smooth muscles *in vitro*, and to exert its impact mainly in the distal urethra[52].

There are 2 meta-analyses examining the effects of CCB and α-1 adrenergic receptor antagonists. Hollingsworth *et al*[31] published a meta-analysis where described cases who received α-blockers or CCBs displayed 65% higher spontaneous calculi transition, compared to the unmedicated group. Guidelines show that cases with a urethral calculus of < 10 mm and well-controlled symptoms can be followed for a while with application of MET as an initial therapy, and recommends α-1 blockers alongside the drugs recommended for MET[49].

In spite of the useful effects of α-1 blockers that have been shown in many studies, there are also studies that report negative effects. Hermanns and Pedro did not find any superiority of α-blockers over placebo in stone expulsion time[53].

Use of corticosteroids in order to decrease edema and inflammation, and thereby ease calculi transition, are under testing. Dellabella *et al*[54], in a small scale study, compared the calculi transition ratio in cases that received tamsulosin with or without the addition of deflazacort. No change was observed in the calculi transition ratio, yet the corticosteroid + tamsulosin group passed their calculus 2 d earlier on average. Larger scale future studies are needed in order for corticosteroids to gain widespread use.

NSAIDs do not provide any benefit in calculi transition time or calculi transition in renal pain[55].

The development of and increasing experience in endoscopic approaches, such as r/f URS, have led to the questioning of whether MET application to urethral stone disease patients admitted with acute renal colic is a loss of time and money. However, recent studies comparing MET and early endoscopic stone removal report less direct and indirect costs with MET, while no difference was detected in hospitalization numbers[56,57].

NUTRITION THERAPY

The etiology of urolithiasis is multifactorial and not always related to nutritional factors. However, nutrition therapy still seems to be useful, either in combination with pharmacological therapy or as a monotherapy. Nutrition therapy involves evaluation of a patient's nutritional state and intake, diagnosis of nutrition risk factors, and the organization and application of a nutrition program[58]. The main target of nutrition therapy is the reduction or prevention of calculus formation and growth *via* decreasing lithogenic risk factors and increasing lithogenic inhibitors in urine.

There are two approaches for nutrition therapy. The first is the empirical approach that is applied to all patients. This approach is a general mixture of various nutrition strategies that target multiple risk factors and that can be applied to patients with no known specific urinary risk factors. The second is the planned/specific approach, and is an alteration aiming to decrease or eliminate specific risk factors of patients. In two studies that included calcium stone patients, the empirical diet side showed a greater decrease in stone recurrence compared to general nutrition, yet these were not compared to direct planned approaches[59,60]. On the other hand, in a study where the empirical and planned nutrition therapy approaches were compared, stone

recurrence rate was reported to decrease with planned therapy[9].

Evaluation of the patient's normal diet and the supplements they use is useful in detecting the effects of an excess, lack, or imbalance of the consumed food or non-food ingredients. A targeted evaluation should be performed in order to detect suitable nutritional factors from the list of foods consumed in the last 24 h provided by the patient in one-to-one conversation or the multi-day nutrition chart kept by the patient.

Hypercalciuria

If sodium intake is identified as a nutritional risk factor, high sodium foods, along with the other foods consumed alongside them, should be examined in preparation for nutritional therapy.

A scale has been developed for predicting the renal acid load capacity (RALC) of foods[61]. This scale calculates the anion/cation ratios of foods, and is accepted as a suitable model in calculating the effects of diet on renal net acid excretion. Foods that carry an acid load proportional to the sulfur amount in their amino acid structures are all meat-based foods (red or white), cheeses (all types), eggs (mostly egg yolks), and grains.

Milk, yoghurt, and fats naturally appear in the RALC scale. Alkaline content foods (those with negative numbers in the RALC scale) are almost all of the fruits and vegetables. A few fruits and vegetables, namely Cornelian cherries (*Cornus mas*) and lentils (*Lens culinaris*), have low acid loads. However, their restriction is not necessary, as their acid loads are far lower than other foods known to have high acid contents. Furthermore, increased fruit and vegetable consumption is usually recommended.

Fiber may reduce gastrointestinal absorption of calcium[62]. If high fiber food consumption is not at the desired levels (25-30 g/d for adult individuals), and calcium and bone statuses look normal, it may be appropriate to recommend higher dietary fiber intake or combination with fiber-reinforced supplements. Caffeine and alcohol may contribute to urinary calcium excretion and thus restriction of these may be useful[63,64].

Some reports show the efficiency of omega-3 fatty acids in reducing urinary calcium excretion[65-67], and supplementation is available *via* current commercial formulations in certain amounts.

Hyperoxaluria

Restriction of food-based oxalate is controversial. The majority of oxalate-containing foods are healthy, and, furthermore, contain special nutrients that frequently have general health benefits and contain fiber, potassium, magnesium, and antioxidants. Restriction or elimination of such foods from the diet will thus do greater harm than good. Reduction of dietary oxalate intake also requires a simultaneous reduction in dietary calcium, as it is essential to maintain the appropriate low calcium/oxalate ratio in the urine, and thus some authors question the low oxalate strategy for this reason.

Specific gastrointestinal microbiota profiles containing separate combinations of bacteria species have been recently identified, and these were observed to be regulated with diet habits[68]. For instance, individuals who consume diets with high fiber content have a different microbiota profile than those that do not[69]. In another study, individuals consuming diets with high meat content were shown to have different bacterial enterotypes than those that consume diets rich in carbohydrates[70]. As related research proceeds, it is possible that some diet patterns (such as oxalate-decreasing bacteria adjusting to suitable concentrations) will be shown to provide anti-lithogenic effects by leading to alterations in enteral microbes.

Hyperuricosuria

If a nutrition evaluation reveals a high content of purine-rich foods, a lack of foods with high purine concentration, and a reduction in the consumption foods with low purine, concentration should be recommended.

Another potential concern is blaming red meat as the only main culprit in uric acid synthesis. Recently, consumption of fish and chicken has also been shown to increase the concentration of serum and urine uric acid to at least the same extent as red meat[71]. As recommending that the patient decrease their red meat consumption will result in a higher consumption of chicken and fish instead, reducing the intake of all these foods is necessary in order to obtain suitable results. Reduction can be organized by decreasing portion sizes and the frequency of consumption during the week.

The quantity of alcohol and fructose consumptions should be evaluated in hyperuricosuria patients, and ways to reduce their intake should be discussed if they are believed to increase stone formation.

Hypocitraturia

When a diet with a high acid load that shows a hypocitraturic effect with its renal citrate reabsorption-improving effect is detected, small amounts of cheese, meat, and other meat products should be recommended in order to lower the acid load[61,72]. For instance, patients usually don't want to eliminate meat and other meat products from their diet, or are unable to apply such a change. Instead, special recommendations to restrict such foods to only small portions in one meal per day will have the same effect. If calorie load is not an issue for the patient, simply balancing the current high acid foods with low acid or alkaline foods (more fruits and vegetables) may be recommended.

Increased dietary intake of citric acid is useful and can increase urinary citrate excretion[40,73-75]. This can be partially achieved *via* the consumption of lemons (which contain concentrated citric acid) and lemonade. Recommendations on increasing consumption of citrus fruits will also provide benefit in terms of increased fiber, potassium, antioxidants, and prebiotics.

Recently, consumption of low sugar and calorie drinks sweetened with citrate and other organic acids has been recommended, as they have the capacity to increase urinary citrate[76]. On the grounds of presenting these drinks as therapeutics targeting the urinary citrate levels in a certain group of patients, liquid volumes provided by these drinks will also contribute to augmentation of overall liquid consumption.

If citrated fruit juices contain mainly citric acid, any bicarbonate obtained is neutralized by hydrogen ions. In that event, the net alkaline response will not take place and the eventual citraturic response will be at a minimum level. In contrast, if potassium accompanies citrate, the net alkaline response will take place, and urinary pH and citrate will rise. Ideal replacement therapy should be low in calories and oxalate, and rich in KCit. Yilmaz *et al*[77] have evaluated tomato, orange, lemon, and mandarin juices in terms of nutritional content. Interestingly, fresh tomato juice contains two times the amount of citrate compared to lemon juice or orange juice; however, the potassium concentration in fresh tomato juice is equal to orange juice and its oxalate content is 40% lower. In the light of these data, although fresh tomato juice seems to be suitable for preventing stone formation, its application is more difficult compared to lemon juice and orange juice. Ripe tomato juice, on the other hand, is rich in sodium.

Haleblian *et al*[78] evaluated 12 different commercial drinks that contained citrate, in an attempt to find natural treatment modalities that are more effective in preventing stone formation. Grapefruit juice was reported to have the highest citrate content, followed by lemon juice, orange juice, lemonade, and Cornelian cherry (*Cornus mas*) juice, respectively.

If frequent diarrhea is thought to contribute to hypocitraturia *via* increased renal citrate reabsorption as a result of excessive bicarbonate loss in the stool, nutrition strategies can be applied that target diarrhea treatment[79]. Probiotic supplements are recommended in the current literature for correction of diarrhea, and many probiotic formulations are commercially available for such use[80,81].

Low liquid consumption

All liquid types induce urinary output, and this is probably the most useful method that can spontaneously reduce the risk of stone formation on its own[8]. Low sugar- and low-calorie drinks are preferred.

Some patients may benefit more from a simple increase in liquid intake than far more specific recommendations. The liquid intake schedule is designed for these situations. The day may be separated into 3 equal parts (of 5 h blocks, for instance, depending on the lifestyle of the patient) and the individual may consume approximately 4 L of (120 oz) liquid by drinking 1200 mL in each part.

Hyperphosphaturia

Phosphate is widely present in all plant and animal-based foods, and so a reduction of dietary phosphate is not practically possible in calcium phosphate stone patients. Control of urinary citrate, calcium, pH, and volume is instead far more important in these patients.

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REVIEW

Pre-treatment considerations in childhood hypertension due to chronic kidney disease

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Abstract

Hypertension (HTN) develops very early in childhood chronic kidney disease (CKD). It is linked with rapid progression of kidney disease, increased morbidity and mortality hence the imperative to start anti-hypertensive medication when blood pressure (BP) is persistently > 90th percentile for age, gender, and height in non-dialyzing hypertensive children with CKD. HTN pathomechanism in CKD is multifactorial and complexly interwoven. The patient with CKD-associated HTN needs to be carefully evaluated for co-morbidities that frequently alter the course of the disease as successful treatment of HTN in CKD goes beyond life style modification and anti-hypertensive therapy alone. Chronic anaemia, volume overload, endothelial dysfunction, arterial media calcification, and metabolic derangements like secondary hyperparathyroidism, hyperphosphataemia, and calcitriol deficiency are a few co-morbidities that may cause or worsen HTN in CKD. It is important to know if the HTN is caused or made worse by the toxic effects of medications like erythropoietin, cyclosporine, tacrolimus, corticosteroids and non-steroidal anti-inflammatory drugs. Poor treatment response may be due to any of these co-morbidities and medications. A satisfactory hypertensive CKD outcome, therefore, depends very much on identifying and managing these co-morbid conditions and HTN promoting medications promptly and appropriately. This review attempts to point attention to factors that may affect successful treatment of the hypertensive CKD child and how to attain the desired therapeutic BP target.

Key words: Anaemia; Childhood; Chronic kidney disease; Hypertension; Hyperparathyroidism; Renin-angiotensin; Vascular calcification

Core tip: Hypertension (HTN) is often difficult to control in chronic kidney disease (CKD). Failure to achieve the desired therapeutic BP target in the hypertensive CKD child could be due to comorbidities and toxic effects of HTN promoting medications. So, before starting or altering anti-hypertensive medications, it is important that patients are evaluated for the roles that HTN promoting medications and co-morbidities like chronic

anaemia, hyperphosphataemia, progressive tunica media calcifications, and serum parathyroid hormone levels that are well above the acceptable limits for CKD stage could be playing in the entire process. Ways of solving this important clinical problem are the focus of this article.

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INTRODUCTION

In the non chronic kidney disease (CKD) paediatric population, hypertension (HTN) is a significant cause of morbidities[1,2] that are further escalated when it co-exists with CKD[3]. HTN develops very early in childhood CKD[3,4]. It is linked with rapid progression of kidney disease hence the Kidney Disease: Improving Global Outcomes recommendation that non-dialyzing hypertensive CKD children should commence antihypertensives when blood pressure (BP) is consistently > 90th percentile and not wait until it is ⩾ 95th percentile for age, gender, and height[5]. Therapeutic BP target in such children, particularly those with proteinuria, should be < 50th percentile for age, gender and height except hypotension is a limitation[5].

Pathophysiology of HTN in CKD is multifactorial and complex. In as much as this is so, the management should not be expected to be simple. An individual with CKD-associated HTN (CKD/HTN) needs to be carefully evaluated for co-morbidities that frequently alter the course of the disease as successful treatment of hypertensive CKD goes beyond life style modification and anti-hypertensive therapy alone. Chronic anaemia, volume overload, endothelial dysfunction, and metabolic derangements like hyperparathyroidism, hyperphosphataemia, 1, 25 $(OH)_2$ vitamin D_3 (calcitriol) deficiency, and tunica media vascular calcification (VC) are some of the co-morbidities that may cause or worsen HTN in CKD. A satisfactory hypertensive CKD outcome, therefore, depends very much on identifying and managing these co-morbid conditions promptly and appropriately. Before initiating a life style modifying plan or any form of antihypertensive treatment, it is important to know if the index patient has: Hyperphosphataemia, secondary hyperparathyroidism (SHPT), endothelial dysfunction, VC, anaemia, volume overload, and an estimated glomerular filtration rate (eGFR) that is < 15 mL/min per 1.73 m^2. Questions should be asked. Will the patient require dialysis? If so, is the patient on calcium-containing phosphate binder? Can the patient be dialyzed with a dialysis fluid that contains the standard concentration of calcium ions (1.75 mmol/L)? The doctor needs to know if the patient is regularly dialyzed or has received a kidney transplant. It is important to know if the patient is on HTN promoting medications like erythropoietin, cyclosporine, tacrolimus, corticosteroids and non-steroidal anti-inflammatory drugs (NSAID). Successful answers to these questions should guide the physician to further steps in tackling the HTN and achieving the therapeutic BP target for the patient.

This review attempts to point attention to factors that may affect successful treatment of the hypertensive CKD child and how to attain the desired therapeutic BP target.

EPIDEMIOLOGY OF HTN IN CKD

High CKD and co-morbidities, including HTN, prevalence have been reported in many studies. Severe CKDs are most commonly associated with the worst co-morbidities. The frequencies of co-morbidities, including HTN, rise with increasing severity of CKD stage[3,4]. Figure 1, generated from data from reference[3], shows the prevalence pattern of HTN by CKD stage in a population of children. Data on CKD incidence and prevalence from different countries vary widely, depending on whether they are hospital-based or obtained from national renal registries. A hospital-based study from Nigeria showed that the overall CKD incidence in children increased from 6.0 in year 2000 to 20.0 per million children population (pmcp) per year in 2009 while the prevalence increased from 8 to 101 pmcp; the incidence and prevalence of severe CKD (eGFR < 30 mL/min per 1.73 m^2) were, however, 3 pmcp/year and 22 pmcp, respectively[3]. Also from Nigeria, another hospital-based study puts the median annual incidence of severe CKD (creatinine clearance, CrCL: < 30 mL/min per 1.73 m^2) at 3.0/million age-related population (MARP) per year with a prevalence of 15 patients per MARP[6]. From a hospital-based study in Jordan, the estimated annual incidence and prevalence of severe CKD were reported to be 10.7/MARP per year and 51/MARP, respectively[7]. An Italian national survey reported a median annual incidence and prevalence of 7.7/MARP per year and 21/MARP, respectively for severe CKD[8]. However, in a French study severe CKD incidence was estimated at 7.5/MARP per year in children younger than 16 years while the prevalence was between 29.4 and 54/MARP[9]. Clearly from the above, the burden of CKD is very high and expectedly, the burden of co-morbidities is also high. The prevalence of HTN in childhood CKD is frequently high; it is reported to range between 20.0% and 80.0%[3,10-13]. This contrasts sharply with the 3.2%-3.6% HTN prevalence in the normal paediatric and adolescents' population[14-16]. Commonly, children with CKD are associated with high nocturnal[17] and masked HTN prevalence[12,13].

Target-organ abnormalities are common features of HTN in children and adolescents. Curiously, CKD children with mild HTN have been reported to have

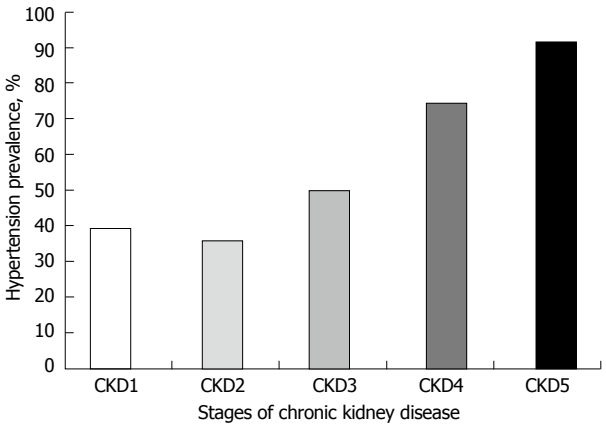

Figure 1 Prevalence of hypertension by chronic kidney disease stage in children. Data for this Figure were obtained from reference[3]. CKD: Chronic kidney disease.

target-organ damage[18-20]. Left ventricular hypertrophy (LVH) is common target-organ damage in HTN[2]. About 34%-38% of paediatric patients with mild and untreated HTN have LVH[21-23]. When associated with proteinuria, HTN has been found to escalate CKD progression and mortality in children and adults[24-26]. In a report, mortality was escalated from 55.5% in non-hypertensive CKD children with heart failure to 84.0% in hypertensive CKD patients with heart failure[3].

It is often difficult to control HTN in CKD. Irrespective of anti-hypertensive medications used, HTN cannot be controlled in more than 50% of children with end-stage renal disease (ESRD)[27-29]. Following treatment with combination antihypertensive medications, only 56% of hypertensive CKD children were able to achieve a BP target of < 50th percentile for age, gender and height[3]. But why is it so difficult to achieve good BP control in hypertensive CKDs? This might be due to failure to critically appraise some of the CKD co-morbidities highlighted above, before starting antihypertensive medications. In a cohort of ESRD children, poor BP control was associated with very young age, post dialysis fluid overload, and hyperphosphataemia. In that report, only 23.5% of treated patients were able to achieve a KDOQI BP target of < 90th percentile[29].

PATHOPHYSIOLOGY OF HTN IN CKD

BP regulation is a complex coordination of physiological functions namely cardiac output, fluid volumes, and peripheral resistance among organ systems in the human body. These organ systems encompass the central nervous system, cardiovascular system, kidneys, and adrenal glands[30]. CKD/HTN develops through a number of complexly interwoven pathomechanisms (Figure 2). Fluid overload and renin-angiotensin-aldosterone-system (RAAS) activation are long recognized important HTN pathophysiological pathways. More recently, increased parathyroid and sympathetic activity and endothelial dysfunction have been reported as contributing to CKD/HTN[31]. HTN may possibly be due to angiotensin Ⅱ (ANG Ⅱ)-related vascular constriction and aldosterone-related sodium retention due to renin hyper secretion by under perfused renal scars/cysts and/or severe renal tissue damage from microangiopathy or tubulointerstitial inflammation[32,33]. Furthermore, high circulating levels of ANG Ⅱ contribute to HTN and end organ injury by promoting mesangial cell proliferation, endothelial cell damage, cardiac enlargement, inflammation, and fibrosis[34]. A further mechanism for CKD/HTN which may be in line with Brenner hypothesis is that reduced nephron number following progressive kidney damage may result in reduced salt and water excretion which may predispose to HTN. The Brenner[35] hypothesis which has since been confirmed in other studies[36,37] is that low sodium excretion with attendant HTN may result from congenital nephron number deficit in the low birth weight infant[35]. While sodium retention and volume overload are established aetiological factors in CKD/HTN, sympathetic hyperactivity remains an important volume-independent cause of HTN whose pathomechanism is unclear[38,39]. Renal afferent signals, dopaminergic abnormalities and leptin accumulation in CKD may be contributory[38,39]. Renal sympathetic nerves in renal tubular epithelial cells and blood vessels are stimulated by ANG Ⅱ to cause an increase in the local release of norepinephrine which then causes renovascular constriction leading to decreased renal blood flow and GFR and HTN[40]. This excessive sympathetic activity is blocked by an ANG Ⅱ receptor blocker (ARB)[41]. Hyperparathyroidism is a common disorder in CKD that interferes with cardiovascular structural geometry and functions. Chronic hyperparathyroidism increases vascular smooth muscle cells' (VSMC) sensitivity to calcium and norepinephrine by promoting calcium ions accumulation within the VSMCs[42,43]. The consequence of this is vasoconstriction and HTN. This action may be countered with calcium channel blockers (CCB)[42,43]. Furthermore, chronic hyperparathyroidism promotes VSMC transformation to osteoblasts and vascular wall mineralization or calcification leading to vascular stiffening, increased peripheral resistance to blood flow with consequent HTN.

Children on maintenance dialysis are reported to have significant incidence of HTN that is as high as 53%-65% and 45%-58% in haemodialysis and peritoneal dialysis patients, respectively[44]. Haemodialysis substantially contributes to HTN by increasing both plasma renin activity and catecholamines[45].

Nitric oxide (NO) is a major vasodilator factor that vascular endothelia secrete, and lack of it causes severe HTN[46]. Endothelium-dependent vasodilatation is impaired in uraemia due to deficient NO synthesis[47]. A circulating endothelium-derived NO synthase inhibitor, presumably asymmetric dimthylarginine, which

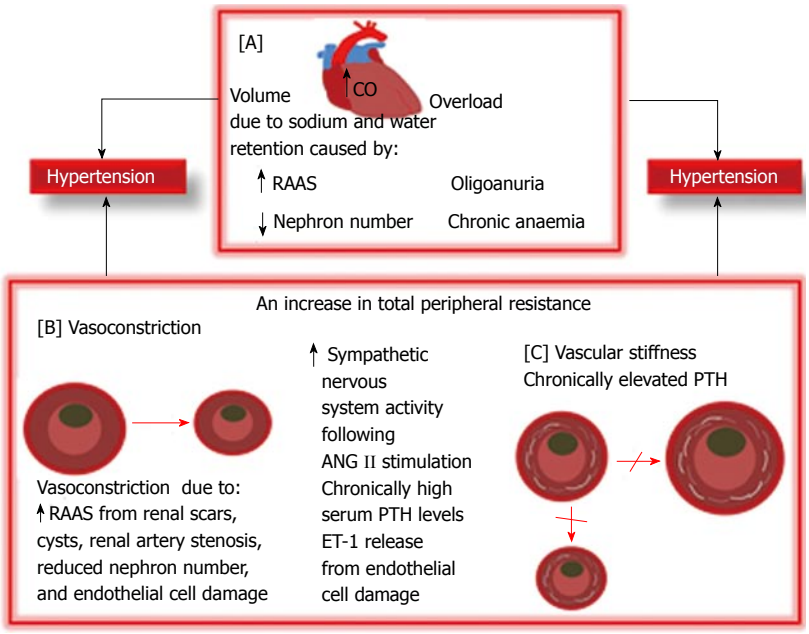

Figure 2 Pathophysiologic mechanisms of hypertension in chronic kidney disease. A: Volume overload is associated with increase in cardiac output (CO) which ultimately leads to hypertension; B: Increase in total peripheral resistance (TPR) due to systemic vasoconstriction leads to hypertension; C: Arterial tunica media calcification causing vascular stiffening and failure of vasodilatation and vasoconstriction are illustrated. Chronic hyperparathyroidism promotes vascular wall mineralization or calcification leading to vascular stiffening and increase in TPR with consequent hypertension. Blood pressure = CO × TPR. RAAS: Renin-angiotensin-aldosterone system; ANG II: Angiotensin II; ET-1: Endothelin 1; PTH: Parathyroid hormone.

accumulates in uraemia is possibly responsible. Endothelin-1 (ET-1), the most potent vasoconstrictor known, is secreted by the vascular endothelium. Plasma ET-1 concentrations rise directly with BP increase in ESRD, suggesting a role for ET-1 in the causation of CKD/HTN[48]. By preventing the breakdown of vasodilatory kinins, angiotensin converting enzyme inhibitors (ACEi) are able to reduce ET-1 expression and suppress ET-1 induced HTN[49,50].

For a number of reasons, CKD patients receive medications like erythropoietin, NSAID, cyclosporine, tacrolimus, and corticosteroids that could predispose to or make HTN worse. These agents cause HTN through a variety of mechanisms that involve interference with arachidonic acid metabolism, ET-1 and NO syntheses. The ultimate result of this interference is HTN through increased TPR due to vasoconstriction with reduced renal perfusion and GFR, increased sodium and water reabsorption as a consequence of RAAS activation. In a review by Krapf *et al*[51], post erythropoietin therapy HTN occurs through increased syntheses of vasoconstrictors like ET-1 and thromboxane (TXB2) but decreased productions of vasodilators like prostacyclin (PGI2) and NO. Reduced production of NO is secondary to decreased expression of endothelium-derived nitric oxide synthase (NOS), an enzyme that catalysis the production of NO. NSAID associated HTN occurs through cyclooxygenase inhibition by preventing arachidonic acid conversion to vasodilator prostanoids like prostaglandin E2 (PGE2) and PGI2[52]. This action leads to increased TPR and volume overload and HTN through increased production of ET-1, increased Na^+ and Cl^- ions reabsorption in the loop of Henle (thick ascending segment) and anti-diuretic hormone-mediated increased water reabsorption. Through another metabolic pathway, NSAID may cause HTN by promoting the release of cytochrome P450-mediated vasoconstricting metabolites of arachidonic acid such as epoxyeicosatrienoic and hydroxyeicosatetraenoic acid[52]. Calcineurin inhibitors, namely cyclosporine and tacrolimus cause HTN through reduced productions of PGI2 and NO but increased productions of ET-1 and TXB2[53] with consequent vasoconstriction, reduced renal blood flow and GFR, sodium and water retention. The mechanism by which corticosteroids causes HTN is not yet clear; however, one of the mechanisms known currently is inhibition of the release of arachidonic acid from phospholipids thereby preventing prostaglandins formation leading to decreased production of vasodilator prostanoids[54]. *In-vitro*, cortisol has been demonstrated to potentiate vascular smooth muscles cells pressor responsiveness to epinephrine and norepinephrine by inhibiting catechol-o-methyl transferase, an enzyme that degrades catecholamines neurotransmitters such as dopamine, epinephrine, and norepinephrine[54]. While, for obvious reasons, these drugs cannot be stopped the dosages can be lowered, in order to achieve good BP control, to levels that will not compromise the primary indications for their prescription.

HTN in the transplanted CKD patient is often caused by volume overload, corticosteroids, and calcineurin inhibitors. ACEi and ARB are avoided in the first few weeks post-transplant to avoid renal insufficiency in the setting of diminished effective arterial blood

volume[55]. To prevent calcineurin inhibitor-induced graft dysfunction, therefore, HTN is treated with CCB in the immediate post-operative period[55]. CCBs like nifedipine and amilodipine have been used with satisfactory outcomes in paediatric transplant patients[56].

WHAT FACTORS MAY PREVENT ATTAINMENT OFTHERAPEUTIC BP TARGET IN CKD-ASSOCIATED HTN?

It is inconceivable that in the setting of chronic anaemia, progressive arteriosclerosis, uncontrolled SHPT, and HTN promoting medications, the therapeutic BP target can be attained in CKD/HTN. Successful HTN treatment outcome demands that these factors be carefully evaluated and managed accordingly.

Volume overload due to chronic anaemia

Anaemia is a frequent comorbidity in childhood CKD[3,4,57]. Failure to attain the target therapeutic BP goal in CKD/HTN may be due to untreated or poorly treated anaemia. Anemia-associated tissue hypoxia causes peripheral vasodilatation. Reduced BP caused by vasodilatation stimulates increased sympathetic activity with attendant tachycardia and increased stroke volume. This is accompanied by increased cardiac output and vasoconstriction. The latter causes reduced renal blood flow, increased RAAS activity and anti-diuretic hormone production leading to salt and water retention[58]. The long term effect of this is HTN or worsening of existing HTN. All hypertensive CKD patients should be carefully assessed for anaemia and volume overload and managed accordingly. Anaemia in childhood CKD is defined as haemoglobin (Hb) concentration < 11.0, < 11.5, and < 12.0 g/dL in children aged 0.5-5, 5-12, and 12-15 years, respectively[57]. It is suggested that when correcting anaemia, the target Hb concentration in all paediatric CKD patients receiving erythrocytes stimulating agent therapy should be maintained within 11.0 to 12.0 g/dL range[57]. Excess volume can be removed with a low ceiling diuretic, like a thiazide, when eGFR is $\geqslant$ 60 mL/min per 1.73 m^2 or with frusemide, a high ceiling diuretic, when eGFR is < 60 mL/min per 1.73 m^2. eGFR $\leqslant$ 15 mL/min per 1.73 m^2 will rarely respond to diuretics. Fluid removal will have to be by dialytic ultrafiltration. It is important to note that when treating anaemia with erythropoietin, HTN may occur following weeks of therapy; this is partly due to increase in the red blood cell mass, increased blood viscosity and resistance to blood flow. Other mechanisms include vascular wall remodeling with resultant rise in vascular resistance[59]. It is also possible that due to direct action of erythropoietin on voltage-independent Ca^{2+} channels in the VMSCs, the sensitivity of the latter to the vasodilatory action of NO may be diminished[60]. Erythropoietin has been reported to exacerbate HTN in both non-dialyzing and dialyzing CKD children[61,62]. This complication can be ameliorated by reducing the dose of erythropoietin.

Tunica media VC or arteriosclerosis

It is a well-known fact that tunica media VC, a form of CKD-mineral and bone disorder, is associated vascular wall rigidity with attendant progressive vascular pulse wave deceleration and abnormal vascular wall geometry. Increasing vascular rigidity ultimately leads to cardiac damage from long standing cardiomyocytes ischaemia, from high oxygen consumption, and diminished coronary blood flow[63]. Dialysis history, consumption of high doses of active vitamin D, deficiencies of inhibitors of calcification, hypercalcaemia and hyperphosphataemia are risk factors for VC in CKD[64]. Hyperphosphataemia is an important and possibly a principal promoter of VC because it has been clearly linked with increased VC and mortality[65,66]. Fibroblast growth factor-23 (FGF23) together with its anti-ageing cofactor, Klotho have been recognized as major regulators of phosphate homeostasis, in addition to inhibiting production and release of parathyroid hormone (PTH) and suppressing renal production of 1, 25 $(OH)_2$ vitamin D. In an experiment by Sitara *et al*[67], FGF23 null mice and Klotho null mice developed similar phenotypes, characterized by very high serum concentrations of phosphate and 1, 25-dihydroxyvitamin D3 with disordered bone mineralization including multiple soft-tissue calcifications. A 13-year-old child with a Klotho gene mutation suffered severe vascular and soft-tissue calcifications, despite markedly elevated serum FGF23. Thus, deficiency of Klotho in this patient prevented FGF23 from exerting its phosphate-lowering effects and its protection against soft tissue calcification[68]. This shows that without Klotho, FGF23 cannot correctly exert its normal physiological functions. Klotho prevents soft tissue calcification by three main mechanisms namely, phosphaturia, kidney function preservation and directly inhibiting phosphate uptake and dedifferentiation by the VSMCs[69]. In CKD, serum levels of FGF23 increase in proportion to the decrease of GFR[70]. This increase can be considered as an appropriate compensatory mechanism in the defense against phosphate retention, in concert with PTH, although it also leads to an inhibition of renal calcitriol synthesis, in contrast to PTH which promotes renal calcitriol synthesis[71]. Of note, chronic dialysis patients and uremic animals have been shown to exhibit a relative resistance to the inhibitory action of FGF23 on parathyroid gland function[72-74]. This is probably due to down regulation of Klotho and FGF23 receptor expression in CKD. Increased systolic BP, resulting in elevated cardiac afterload and LVH and decreased diastolic BP and impaired coronary perfusion are initial major consequences of arterial stiffening[75]. Cardiovascular calcification (CVC) is not only a progressive disorder; it is also severer among CKD patients, with poorer cardiovascular outcome, compared with other populations[76]. VC must, therefore, be recognized very early in CKD and aborted as progression will worsen both the kidney disease and HTN thereby making BP

therapeutic goal unattainable with dire consequences for the patient. High pulse pressure suggests arterial stiffening/rigidity and therefore, should be an indication for anyone or combination of the following investigations: flow mediated dilation for endothelial dysfunction, carotid intimal medial thickness (cIMT), pulse wave velocity (PWV) and echocardiography for valvular calcification; plain X-rays of the hands including the wrists can also detect VC in the radial and digital arteries[76,77]. Similarly, lateral lumbar spine (lateral abdominal X-ray) and pelvic radiographs can detect VC in the abdominal aorta and femoral and iliac arteries[64]. However, in detecting and quantifying CVC, including the coronary arteries, the electron-beam computed tomography (EBCT) and multislice CT (MSCT) are the most sensitive radiologic techniques available[78-82]. cIMT, PWV, EBCT and MSCT are established indicators of structural and functional anomalies of blood vessels, including calcification in children and adults[78-82]. cIMT in paediatric CKD patients was adversely affected by high plasma phosphate[78-80]. In 85 dialyzing children, the cIMT increased by 0.15 mm for each mmol/L rise in the serum phosphate concentration[78].

Can VC be treated or reversed?

Currently, there is no definitive treatment for VC reversal but the process leading to it can be halted through preventive measures. The most important preventive measure is to ensure that serum phosphorous level is kept within the normal age-specific range. The approaches to reducing high plasma phosphate level should include reducing dietary phosphate intake[83], and gastrointestinal absorption with phosphate binders[84], and giving more dialysis to increase clearance in those with 5D-CKD[85,86]. Stages 3-5 CKD patients can have their serum phosphorous kept within acceptable limits of 0.81-1.45 mmol/L (2.5-4.5 mg/dL); high values should, however, be brought down to the normal limits in CKD-5D. On the other hand, serum calcium should be kept within the normal limits of 2.1-2.6 mmol/L (8.8-10.5 mg/dL) in individuals with 3-5D CKD[85,86]. However, a dialysate fluid having low calcium concentration of 1.25-1.50 mmol/L (2.5-3.0 mEq/L) is advised for use in order to avoid hypercalcaemia, adynamic bone disease and rapid VC progression that may occur with the standard dialysate fluid, containing 1.75 mmol/L of calcium, when used in CKD-5D[76]. It is recommended that serum concentrations of calcium, phosphorus, PTH, and alkaline phosphatase should be determined starting from CKD-2 in paediatric patients[76]. Furthermore, it is suggested that serum calcium and phosphorous be measured in CKD 3, CKD 4, and CKD 5/5D at 6-12, 3-6, and 1-3 mo intervals, respectively[76]. In hyperphosphataemic individuals with 3-5D CKD, calcium-based phosphate binders are best avoided when there is evidence for arterial calcification and/or adynamic bone disease and/or persistently low serum concentrations of PTH. Calcium-based phosphate binders and/or calcitriol or vitamin D analog are similarly contraindicated when such patients have hypercalcaemia that is persistent or recurrent[76]. Increased dialytic phosphate removal is suggested for CKD stage 5D if hyperphosphataemia is persistent. Effective alternatives to calcium-based phosphate binders include non calcium-based phosphate binders like sevelamer, and lanthanum salts. Although Sevelamer hydrochloride possesses the additional benefit of reducing total cholesterol and low density lipoprotein cholesterol concentrations in the plasma, patients may need to be on calcium supplement when there is overt hypocalcaemia[76]. Sevelamer hydrochloride has been reported in some studies to attenuate arterial calcification progression in stages 3-5 and 5D CKD patients when compared to similar patients treated with calcium-based phosphate binders[87-91]. Zhang *et al*[92] have shown in their systematic review of literature on adult patients that lanthanum carbonate efficaciously reduces serum phosphorus and intact PTH levels without raising the serum calcium concentration. The author is currently not aware of any published study on lanthanum carbonate use in children.

The use of pyrophosphate, bisphosphonate and thiosulfate in the prevention of VC is largely experimental. With current level of information available from various experimental studies, they show a lot of future promise for the prevention of VC in humans when they become clinically available. Schibler *et al*[93] were able to demonstrate that high dose pyrophosphate could inhibit tunica media calcification in rats that were intoxicated with vitamin D. High dose pyrophosphate was used to prevent its rapid hydrolysis to orthophosphate. However, to obviate the need for high dose pyrophosphate, bisphosphonate a non hydrolysable analogue of the former was developed. Medial calcification has been effectively inhibited with bisphosphonate in uraemic rats[94]. Pasch *et al*[95] demonstrated that tunica media calcification developed within four weeks in a Wister rat model of uraemic renal failure caused by adenine diet-induced severe interstitial nephritis. Using thiosulfate at doses and frequencies that were similar to that used in patients with calcific uraemic arteriolopathy, Pasch et al were able to completely prevent VC in their animal model. However, the drawbacks with the thiosulfate study of Pasch *et al*[95] are that: (1) the mode of action is unknown; (2)thiosulfate prevents but does not reverse VC; (3) its safety limits in man are unknown; and (4) there is the possibility of reduced bone mineralization.

VC is a common complication of high doses of vitamin D receptor agonists (VDRAs) especially when associated with hypercalcaemia[96-99]. However, using lower doses of VDRAs that are currently in use in clinical practice, Lau *et al*[100], were able to demonstrate that active vitamin D (calcitriol, 30 ng/kg) and its analog (100 ng/kg paricalcitol) prevented arterial medial VC in CKD mice given high phosphate diet (1.5%). Independently of serum calcium and PTH both VDRAs reduced the degree of VC *via*: (1) elevated serum Klotho, increased phosphaturia as well as normalized serum phosphate and FGF23 levels; and (2) up regulation of VSMC osteopontin but reduced

circulating osteopontin that is associated with VC reduction. Using much lower (physiological) dosages, Mathew *et al*[97] had earlier noted that both calcitriol and paricalcitol prevent VC. The clinical benefit of both studies with regard to VC needs to be determined by further studies.

SHPT

As discussed above, hyperparathyroidism causes HTN through vasoconstriction and vascular medial wall calcification[42,43]. PTH level should be determined early in the course of managing CKD/HTN as this may be elevated beyond the expected level for the CKD stage in the patient. Appropriate management of the inappropriately elevated PTH for CKD stage may impact significantly on HTN outcome. In children with CKD, 25 (OH) vitamin D (calcidiol) is a common deficiency; it is one of the factors that may be responsible for SHPT in CKD. The serum level of calcidiol (normal: 8-50 ng/mL) should be determined at baseline in every CKD patient. The ways by which active vitamin D sterols suppress PTH levels include: Increased intestinal calcium absorption, and PTH gene transcription suppression. Given either in daily or intermittent doses, calcitriol and alfacalcidol effectively suppress PTH and improve growth in childhood CKD[101,102]. Hypercalcaemia is, however, a serious side effect especially when ingested with phosphate binders containing calcium. The newer vitamin D analogues namely 22-oxacalcitriol, 19-nor-1, 25-dihydroxy vitamin D2 (paricalcitol) and 1α-hydroxyvitamin D2 (doxercalciferol) are associated with minimal intestinal calcium and phosphorus absorption. PTH levels are effectively reduced by doxercalciferol and paricalcitol; both have the ability to reduce serum calcium levels better than calcitriol in CKD children and adults[103,104]. Where SHPT is due to hyperphosphataemia, appropriate use of phosphate binders may just be sufficient. Cinacalcet is a type II calcimimetic that allosterically modulates the calcium sensing receptor, CaSR thus making it more sensitive to circulating calcium ions with resultant reduction in PTH release[105]. Studies have shown that calcimimetics effectively act on the parathyroid gland of CKD-5 patients to promote reasonable decreases in circulating serum phosphorus and calcium ions[106,107]. Calcimimetics have on the other hand been associated with unwanted increases in serum phosphorus, through unknown pathways, in CKD-3/4. They should, therefore, be avoided in such patients[108,109]. Calcimimetics have been found useful in the few paediatric CKD-5 patients studied so far[110,111]. Six CKD 5D children aged between 11 mo and 14 years who had uncontrolled SHPT and treated with cinacalcet (doses: 0.4-1.4 mg/kg) showed satisfactory and sustained correction of the hyperparathyroidism[112]. Whatever medication that is chosen for the hyperparathyroidism, it is suggested that the target serum PTH in CKD 3, CKD 4, and CKD 5/5D should, respectively be in the 35-70, 70-110, and 200-300 pg/mL range to avoid adynamic bone disease from too low serum PTH[113]. In CKD, the serum PTH should be maintained within 2-9 times the upper limits of the normal laboratory range[76]. It is important that serum PTH and alkaline phosphatase are determined at baseline, every 6-12, and 3-6 mo, respectively in patients with progressive CKD 3, CKD 4, and CKD 5/5D[76].

CONCLUSION

The pathomechanism of HTN in CKD is multifactorial and complexly interwoven. Successful treatment of HTN in CKD, therefore, goes beyond life style modification and anti-hypertensive therapy alone. The patient with CKD/HTN needs to be carefully evaluated for co-morbidities that frequently alter the course of the disease. It is also important to know if the HTN is caused or made worse by the toxic effects of medications like erythropoietin, cyclosporine, tacrolimus, corticosteroids and NSAID. A satisfactory therapeutic outcome in the hypertensive CKD, therefore, depends very much on identifying and managing these co-morbid conditions promptly and appropriately.

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MINIREVIEWS

Hepatorenal syndrome: Update on diagnosis and treatment

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Abstract

Acute kidney injury (AKI) is a common complication in patients with end-stage liver disease and advanced cirrhosis regardless of the underlying cause. Hepatorenal syndrome (HRS), a functional form of kidney failure, is one of the many possible causes of AKI. HRS is potentially reversible but involves highly complex pathogenetic mechanisms and equally complex clinical and therapeutic management. Once HRS has developed, it has a very poor prognosis. This review focuses on the diagnostic approach to HRS and discusses the therapeutic protocols currently adopted in clinical practice.

Key words: Hepatorenal syndrome; Cirrhosis; Acute kidney injury; Diagnosis; Treatment; Terlipressin; Liver support system

Core tip: Hepatorenal syndrome is a functional and potentially reversible form of kidney failure. The pathophysiological bases of this disease are complex and not fully understood. The aim of this review is to focus the current diagnostic approach and the updated therapeutic protocols adopted in clinical practice.

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PATHOGENESIS

Hepatorenal syndrome (HRS) can be considered the final stage of a pathophysiological condition charac-

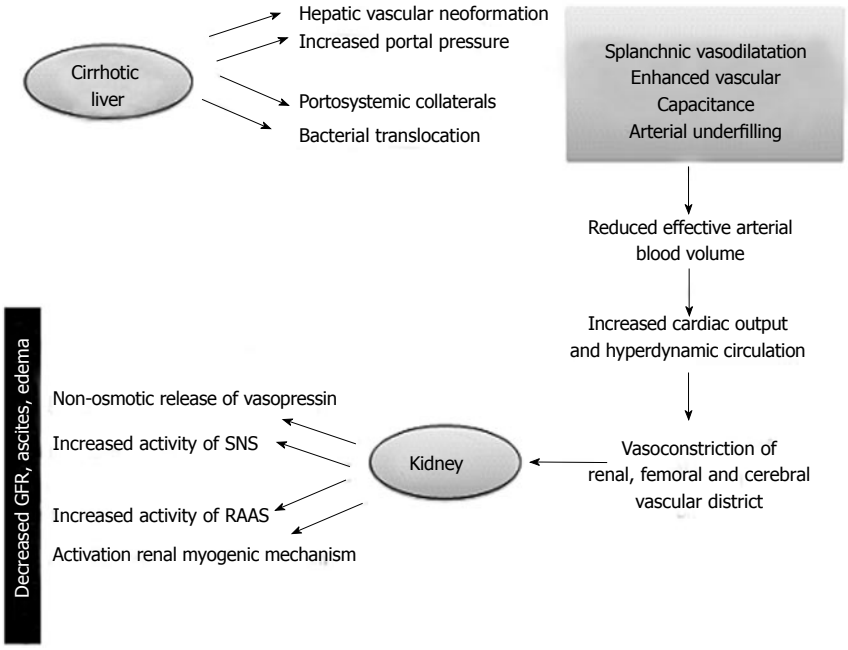

Figure 1 Hepatorenal syndrome: Pathogenesis. In cirrhotic patients portal hypertension can lead to markedly dilated splanchnic arterial vessels. The bacterial translocation of intestinal germs, the gradual decrease in systemic vascular resistances, the hepatic vascular neoformation are potential risk factors. The fall in mean arterial pressure is compensated by increase in cardiac output and by activation of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) to improve systemic vascular resistence. The response mechanisms to the decreased effective circulating volume caused by Enhanced vascular capacitance (so-called "arterial underfilling") include the non-osmotic release of vasopressin accounting for renal tubular sodium resorption and water retention leading to the onset of ascites, edema and hypervolemic hyponatremia. These compensatory mechanisms ultimately have repercussions on kidney function causing reduced glomerular filtration rate (GFR) and further water retention thereby worsening the water overload.

terized by decreased renal blood flow resulting from deteriorating liver function in patients with cirrhosis and ascites[1-5].

Hemodynamic changes associated with endothelial shear stress occur before the onset of ascites and are sustained by an increase in pro-angiogenic factors like the vascular endothelial growth factor and platelet-derived growth factor and vasodilators (carbon monoxide, endocannabinoids and nitric oxide) able to promote the formation of hepatic, splanchnic and portosystemic collateral vessels[6-11] (Figure 1).

The ensuing hemodynamic instability may give rise to many clinical events that further interfere with the compensatory mechanisms. These include the onset of spontaneous bacterial peritonitis, gastrointestinal bleeding and post-paracentesis circulatory dysfunction[12].

The renal impairment is worsened by a progressive cardiac dysfunction known as cirrhotic cardiomyopathy. The latter is characterized by diastolic impairment with septal ventricular hypertrophy, blunted ventricular response to stress, systolic and diastolic dysfunction, and electrophysiological abnormalities (prolongation of QT interval)[7]. Systolic dysfunction is due to impairment of both β-adrenergic receptor and increasing in endogenous cannabinoids and cardiosuppressants such as nitric oxide and inflammatory cytokines and myocyte apoptosis. Furthermore it is possible that several intracellular signaling pathways are involved.

On the other hand the activation of renin-angiotensin system and salt retention play a role in diastolic disfunction. Recent studies have stated myocardial dysfunction in cirrhosis as a contributing, or even a precipitant factor, of HRS[13,14] .

EPIDEMIOLOGY

According to Fede *et al*[15], approximately 20% of cirrhotic patients with diuretic-resistant ascites potentially develop HRS, while a prospective study by Ginès *et al*[4] on 229 patients with cirrhosis found an 18% incidence of HRS at one year, rising to 39% at five years after initial diagnosis.

HRS may also arise in patients with acute liver failure as shown in Akriviadis *et al*[16]: They considered 101 patients with alcoholic hepatitis of whom 28 developed HRS after a four-week follow-up. Planas *et al*[17], in a study enrolling 263 cirrhotic patients with a follow-up of 41 ± 3 mo after the onset of ascites, found prevalence rates of 2.6% and 5% for HRS types Ⅰ and Ⅱ respectively, with a cumulative probability of 11.4% at five years. The prevalence of HRS increases with liver disease progression, Wong *et al*[18] reporting a rate of 48% in patients on the waiting list for liver transplant.

Despite discrepancies in literature data, the prevalence of HRS has dropped in recent years, probably as a result of a better understanding of its pathophysiology and improved clinical management[19]. Nonetheless the long-term survival of HRS patients remains poor and the only effective treatment for this condition is liver transplantation.

Table 1 Diagnostic criteria for hepatorenal syndrome

Cirrhosis with ascites
Serum Creatinine > 1.5 mg/dL
Absence of shock
No improvement of serum creatinine (decrease to a level of 1.5 mg/dL or less) after at least 2 d of diuretic withdraw and volume expansion with albumin (The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/d)
No current o recent exposure to nephrotoxic drugs
Absence of parenchymal disease as indicated by proteinuria > 500 mg/d, microscopic hematuria (50 red blood cells per high power field) and abnormal renal ultrasonography

HRS: Hepatorenal syndrome.

Table 2 Characteristics of type Ⅰ and type Ⅱ hepatorenal syndrome

HRS I	Doubling of serum creatinine in < 2 wk	A precipitating event is present in the most of case	No history of diuretic resistant ascites	10% survival in 90 d without treatment
HRS II	Renal impairment gradually progressive	No precipitating events	Always ascites diuretic resistance	Median survival 6 mo

HRS: Hepatorenal syndrome.

DIAGNOSIS

The diagnostic criteria for HRS were initially defined by the International Ascites Club (IAC) in 1994[20-22]. Since then, advances in our understanding of HRS pathogenesis and the introduction of new therapies led to repeated revisions of the criteria. The latest version of 2007 excludes the use of creatinine clearance (due to its poor correlation with kidney function in patients with cirrhosis), and has eliminated minor criteria (sodium excretion fraction, urinary output) deemed less sensitive and specific. Concomitant bacterial infection does not rule out a diagnosis of HRS but it is crucial to identify the absence of septic shock[1] (Table 1).

Two forms of HRS, types Ⅰ and Ⅱ, have been described. They differ in severity and rate of progression and can be considered two separate clinico-pathological entities[23] (Table 2).

Type Ⅰ HRS is characterized by acute onset and rapidly progressing kidney failure with a doubling of serum creatinine to > 2.5 mg/dL (corresponding to a 50% reduction in the creatinine clearance rate) in less than 2 wk, usually associated with multiorgan damage. The prognosis is poor with only 10% of patients surviving longer than 90 d[4].

This type of HRS can develop spontaneously but more often tends to follow a precipitating event, mostly spontaneous bacterial peritonitis or other infections like pneumonia, urinary tract infections or cellulitis[24]. Other potential risk factors include viral, alcoholic, toxic or ischemic hepatitis (*e.g.,* TIPS), gastrointestinal bleeding and surgical procedures (Table 3).

Type Ⅱ HRS represents the final kidney response to hemodynamic impairments in cirrhosis. This type presents as a less severe and more gradual decline in renal function associated with refractory ascites. The increase in creatinine is gradual with mean values of 1.5-2.0 mg/dL. Type Ⅱ HRS predisposes patients to the development of type Ⅰ HRS after a precipitating event. The average survival rate is six to eight months after onset.

The differential diagnosis between the two types of HRS is based on the rate of progression and extent of renal impairment, whereas the pathophysiological differences have not yet been fully clarified.

A spontaneous recovery is rare in both cases unless there is a significant improvement in liver function.

The differential diagnosis between HRS, other causes of kidney disease and septic shock remain extremely difficult. Despite the widespread circulation of the IAC criteria, a serum creatinine cut-off of 1.5 mg/dL appears limited as it does not take into account its physiological fluctuations. In addition, creatinine values ≤ 1.5 mg/dL may overestimate the true reduction in GFR[25].

The AKI network (AKIN) has proposed a new definition of AKI for the diagnosis of HRS designed to implement the traditional IAC criteria for prompt recognition of kidney damage. AKI is defined as the abrupt loss of kidney function resulting in a 0.3 mg/dL increase in serum creatinine in 48 h or a 50% increase over the basal value. The aim is to apply the AKI criteria to decompensated cirrhotic patients for an early identification of kidney failure and thereby implementing prompt aggressive treatment[26].

Two recent prospective studies assessed the applicability of the AKI criteria in patients with cirrhosis. The study by Fagundes *et al*[27] on 375 patients and another by Piano *et al*[28] on 233 cirrhotic patients both divided the populations into two groups based on kidney function. The first group comprised patients with a serum creatinine increase ≥ 0.3 mg/dL but below the threshold of 1.5 mg/dL, whereas the second enrolled patients with creatinine > 1.5 mg/dL. In both cases renal decline and mortality rates were significantly higher in the group with serum creatinine > 1.5 mg/dL, with a lower probability of kidney disease regression. These results suggest that AKI with serum creatinine values < 1.5 mg/dL is a relatively benign and potentially reversible condition, whereas the progression of renal deterioration to a significant decrease in GFR (values > 1.5 mg/dL) carries a poor prognosis[27,28].

Nonetheless, a recent editorial by Arroyo *et al*[29] pointed to a lack of evidence demonstrating the real advantage of the IAC guidelines with respect to AKI criteria. The stratification of cirrhotic patients according to single organ damage (kidney, liver or brain) appears to simplify the complex changes occurring in patients with decompensated liver failure.

Mindikoglu *et al*[2] proposed a new classification

Table 3 Risk factors for the onset of hepatorenal syndrome

Spontaneous bacterial peritonitis
Large volume paracentesis (> 5 L) with inadequate albumin substitution
NSAID and other nephrotoxic drugs, iv contrast
Bleeding from esophageal varices
Post TIPS syndrome
Diuretic treatment

Spontaneous bacterial peritonitis are leading trigger of HRS. One-third of patients with SBP develop HRS in the absence of septic shock. Diuretic treatment has been suggested as a potential trigger of HRS, but there are no clear supportive data for this. HRS: Hepatorenal syndrome; NSAID: Non-steroidal anti-inflammatory drug; TIPS: Transjugular intrahepatic portosystemic shunt.

associating GFR measurement and renal blood flow to stratify renal dysfunction, introducing the new concept of "pre-HRS", *i.e.,* patients with reduced renal blood flow but still normal or slightly reduced GFR. However, further studies are required to establish the clinical utility of this concept[30].

In all patients with acute renal failure and even more in patients with cirrhosis, serum creatinine may not reflect the reduction of kidney function with a significant difference between male and female. Because of that it was proposed using cystain C as alternative marker of renal function.

Seo *et al*[31] and Sharawey *et al*[32] showed that serum cystatin C level is a good marker for predicting HRS and survival in patients with cirrhotic ascites.

In the last 2 years the IAC organised a consensus development meeting in order to analyse the new definition of AKI in patients with cirrhosis and HRS: All the experts agreed on the removal of a fixed cut-off value of serum creatinine from the diagnostic criteria of HRS and they didn't suggest to evaluate Cystain C determination[33] (Table 1).

As there are currently no specific tests to identify HRS, diagnosis rests on the exclusion of other causes of kidney failure. It is important to establish the etiology of kidney injury in order to institute the appropriate treatment.

The onset of AKI in patients with cirrhosis enters into the differential diagnosis with other forms of kidney injury: Pre-renal (45%), organic, including acute tubular necrosis and glomerulonephritis (32%), and less frequently obstructive nephropathy (< 1%)[34,35] (Table 4).

The parameters traditionally used to distinguish AKI from chronic kidney disease (CKD) (urinary sodium concentration, serum and urine osmolarity) are not applicable in patients with cirrhosis and ascites. Likewise, serum urea values are usually reduced in cirrhotic patients due to the impaired hepatic synthesis.

Belcher *et al*[36] proposed the use of urinary biomarkers of AKI to improve the diagnostic process: urinary levels of neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), kidney injury molecule-1 and liver fatty acid-binding protein are elevated in liver disease patients with kidney injury due to acute tubular necrosis.

Table 4 Differential diagnosis of renal failure in cirrhosis

Pre-renal	History of fluid loss, gastrointestinal bleeding, treatment with diuretics or non-steroidal anti-inflammatory drugs
Organic	Medical history, laboratory tests (cryoglobulinemia, complementemia, *etc.*)
Obstructive	Ultrasound imaging
Chronic kidney disease	Anemia, proteinuria, secondary hyperparathyroidism, ultrasound evidence of renal cortical thinning

Two recent trials studied patients admitted to hospital for cirrhosis-induced complications. They both demonstrated that raised urinary levels of NGAL may serve to distinguish functional kidney damage from acute tubular necrosis or necrosis arising in HRS[37,38].

Barreto *et al*[39] confirmed that urinary NGAL predicts clinical outcome, namely persistent kidney injury and mortality at three months in hospitalized patients with cirrhosis and bacterial infections. Although further clinical trials are required, NGAL appears to predict short-term mortality in cirrhotic patients.

Renal biopsy is not used for diagnostic purposes but can be entertained when a decline in renal function is associated with active urinary sediment or clinical status not corresponding to IAC criteria or unresponsive to therapy.

TREATMENT

Despite improvements in the clinical management of HRS patients in the past twenty years, currently available treatments enhance patients' short-term survival but offer little benefit in the longer term.

The current therapeutic armamentarium includes drugs with specific vasoconstrictive effects on the splanchnic circulation in addition to renal and liver replacement therapies which can be artificial or natural (liver transplantation). Liver transplant remains the only truly effective treatment but is limited by the high mortality rate in HRS patients and the shortage of available organs.

A recent literature review by Fabrizi *et al*[40] noted that pre-transplant kidney function is the most important predictor for patient survival after liver transplant. Pharmacological treatment and medical care serve as a "bridge" to transplant to improve the patient's prognosis.

Prevention and general patient management

The cirrhotic patient with ascites must be closely monitored to prevent and treat precipitating factors[41-45] (Table 5).

If multiorgan damage is present, some patients, especially those with type I HRS, may require a high level of care, and admission to an intensive care facility. In addition, a patient-tailored diet and physical rehabi-

Table 5 Prevention of hepatorenal syndrome and general patient management strategies

Avoid drugs that reduce renal perfusion or nephrotoxic substances
Minimize exposure to organ-iodated contrast agents
Intravenous albumin is recommended for volemic filling after large volume paracentesis (8 g of albumin for each liter of ascites removed)
Diuretic therapy should be suspended
Pentoxifylline as drug's anti-TNFa activity
Antibiotic prophylaxis to prevent infections reducing intestinal bacterial translocation (norfloxacin 400 mg/d)
Intravenous albumin administered in association with ceftriaxone in SPB
Adrenal insufficiency should be identified and treated
Drug dosages must be adjusted according to renal function

ligation program should be planned and each patient assessed for eligibility for liver transplantation to avoid aggressive treatment.

The aim of treatment must be to stabilize patients until liver transplantation and optimize their clinical condition for a successful transplant[6].

Medical management

Medical management is targeted at the pathogenetic mechanisms underlying HRS. The ideal treatment is designed to improve liver function by exerting splanchnic vasoconstriction and renal vasodilation to reduce portal hypertension and raise systemic arterial pressure[34]. The specific drug approach is based on the use of vasoconstrictor agents (terlipressin, norepinephrine, midodrine) to correct circulatory changes.

As reported in a review by Davenport *et al*[41], intravenous administration of terlipressin and albumin is currently the treatment of choice for patients with type Ⅰ and type Ⅱ HRS, resulting in an overall reduction in short-term mortality rates.

The vasopressin synthetic analogue terlipressin is a V1 agonist of the receptors expressed on vascular smooth muscle cells in the splanchnic circulation. It is enzymatically transformed from the inactive to biologically active form (lysine-vasopressin) with a longer half-life than other vasopressin analogues, *e.g.,* ornipressin. Terlipressin's long half-life accounts for its initial administration as an intravenous bolus, now replaced by continuous infusion[46,47]. The vasoconstrictive effect of terlipressin corrects the circulatory dysfunction typical of end-stage liver disease, indirectly rebalancing intrarenal vasoconstriction and lowering levels of renin, noradrenaline and ultimately serum creatinine. As a result, the kidney regains control of its self-regulatory system. In addition, terlipressin has a major impact on the portal circulation reducing portal venous flow and porto-systemic pressure with a concomitant increase in hepatic arterial blood flow and an improvement in hepatocellular oxygenation.

Terlipressin can be administered as an intravenous bolus starting from a dose of 0.5 mg every 4-6 h or as a continuous infusion (2 mg/d). The dosage can be doubled after three days of treatment if there is no improvement in serum creatinine (*i.e.,* a reduction of at least 25%)[12]. The total daily dose should not exceed 2 mg Ⅳ bolus every 4-6 h or 12 mg/d in continuous infusion[40]. Continuous infusion is associated with a better clinical response and fewer side-effects[48].

Terlipressin should be associated with albumin (at a dose of 1 g/kg per day on the first day, without exceeding 100 g/d, followed by 20-40 g/d). Albumin serves to expand the circulating plasma volume by raising the oncotic pressure. In addition, it has metabolic, immune and vasoconstrictor effects by binding to endotoxins, nitric oxide, bilirubin and fatty acids[49,50]. The terlipressin-albumin association improves renal function by 40%-60%[48], increasing the number of patients eligible for liver transplant thereby enhancing their outcome[51-53]. When serum creatinine values reach < 1.5 mg/dL, treatment is deemed complete[48]. The average recovery time is seven days up to a maximum of two weeks after which terlipressin should be suspended if there is no improvement in kidney function[54]. Even when there is a complete response, HRS recurrence is common (50% of cases) and treatment should be resumed.

Terlipressin has an acceptable side-effects profile. Side effects include abdominal pain with cramps and diarrhea until intestinal ischemia; cardiac tachiarrhythmias and chest pain can be observed, in generale ECG monitoring is recommended. Vasoconstriction induced by terlipressin may cause also cyanosis, livedo reticularis, necrosis of the skin and extremities[53]. Terlipressin could also associated with hyponatremia but without impairment of patients' survival[55].

If patient shows side effects the dosage should be reduced or administration discontinued. Continuous infusion is safer and less burdened by side effects[52].

The incidence of ischemic events ranges from 5% to 30% even though many studies exclude patients at risk of cardiovascular ischemia. Fabrizi *et al*[56]'s literature meta-analysis of 243 patients compared the effects of terlipressin *vs* placebo on kidney function and survival in HRS patients. Their data confirm the regression of HRS in a significant number of treated patients but no effect on survival rates.

The association albumin and terlipressin showed an improvement of survival rates for positive effects of albumin on cardiac function, on the reduction of nitric oxid and on improving the responsiveness of arterial wall to vasoconstrictors. Other studies in patients treated with terlipressin and differents colloids didn't showed the same positive response[52,53].

Terlipressin is not available in the United States and Canada so therapeutic protocols with other vasoconstrictor agents need to be considered in those countries.

The alpha-adrenergic receptor agonist norepinephrine has proved effective in the treatment of HRS. Continuous norepinephrine infusion (at a dose of 0.5-3 mg/h) must be associated with albumin administered as an Ⅳ bolus at least twice daily (1 g/kg up to a maximum of 100 g/d). The aim is to raise mean

arterial pressure by 10 mmHg and urinary output > 200 mL every four hours. The maximum period of treatment must not exceed 2 wk[57,58].

A pilot study by Ghosh *et al*[59] compared terlipressin *vs* noradrenaline in 46 patients with type Ⅱ HRS. Neither treatment proved superior to the other and the outcome was broadly the same in terms of HRS regression. Noradrenaline can be deemed as effective as terlipressin but its lower costs makes it an interesting option for the treatment of HRS.

Another alpha-adrenergic agent, midodrine, can be considered a good alternative to terlipressin and is the drug most commonly used in the United States. Midodrine is a prodrug metabolized by the liver into its active metabolite (desglymidodrine) and then excreted in the urine. When administered in association with octreotide (a somatostatin analogue and splanchnic vasodilator) it has a positive effect on renal function in HRS patients with 50% likelihood of disease reversal[49,60-62].

Midodrine can be administered orally (initial dose 7.5 mg every 8 h up to a maximum of 12.5 mg three times daily) or octreotide can be given by continuous infusion (50 mcg/h) or subcutaneously (from 100 to 200 mcg 12.5 mg three times daily). Albumin must be associated at the usual dose[6]. Midodrine dosage has a major effect on its effectiveness: Patients treated at the maximum dose have shown a complete response to therapy, whereas octreotide administered alone has no effect on kidney function[62].

Transjugular intrahepatic portosystemic shunt

The creation of a portosystemic shunt to treat refractory ascites can improve renal function in cirrhotic patients as it increases venous return of splanchnic blood to the right heart thereby raising the effective arterial blood volume and reducing hepatic sinusoidal pressure. Although literature reports on the use of transjugular intrahepatic portosystemic shunt (TIPS) in HRS patients are scant, Brensing *et al*[63] analyzed the trend of creatinine clearance in patients treated with TIPS, finding a twofold increase in clearance values from 9 to 27 mL/min two weeks after the procedure. Despite its side-effects (namely the high incidence of hepatic encephalopathy), TIPS can be used in the short term to gain potential benefits in patients awaiting liver transplant[64,65].

Renal replacement therapy

The indications for renal replacement therapy (RRT) in patients with HRS are the same as those for AKI patients without cirrhosis. HRS patients, particularly those with type Ⅰ, may need to undergo dialysis because of metabolic acidosis or hyperkalemia due to water or sodium retention or less frequently uremic intoxication.

RRT is among the so-called bridging therapies designed to support patients awaiting liver transplant, but there is no evidence that dialysis improves the long-term survival of patients not eligible for transplantation[66].

By definition, patients with cirrhosis are at higher risk of bleeding and hemodynamic complications (hypotension, arrythmias) hampering the decision to initiate and manage dialysis treatment. Cirrhotic patients on RRT have a 2%-8% higher mortality rate than other patients[67].

Continuous renal replacement therapy (CRRT) is usually preferred to intermittent dialysis due to its greater hemodynamic stability ensuring fewer fluctuations in intracranial pressure. However, prospective studies show that the choice of RRT has no significant effect on survival rates in patients awaiting liver transplantation[68-71]. Anticoagulation of the extracorporeal circuit is needed to maintain the filter patency without increasing the risk of hemorrhage. Regional citrate anticoagulation emerged as possible alternative but no specific protocols are currently recommended for patients with liver diseases[72].

Peritoneal dialysis is an option to resolve ascites and correct other complications of cirrhosis without exposing patients to the complications of hemodialysis[73,74].

The precise timing and dose of RRT have yet to be established but some studies demonstrate that the early initiation and maintenance of a constantly negative fluid balance have a positive effect on survival rates[75].

Extracorporeal artificial liver support therapy

More complex therapies known as liver support measures may be required to replace the liver's detoxifying system. RRT removes water-soluble toxins whereas most of the molecules accumulated in the course of liver failure are linked to albumin and hence are not removed by conventional hemodialysis.

Liver support systems are designed to enhance and optimize these results, increasing the removal of water-soluble toxins and those linked to albumin.

To date these treatments have served as bridging therapies for patients awaiting liver transplantation.

Molecular adsorbent recirculating system

Molecular adsorbent recirculating system (MARS) combines the conventional CRRT monitor or a standard hemodialysis machine with an albumin dialysate circuit. The system is based on the removal of albumin-bound toxins (bile acids and nitric oxide) and water-soluble cytokines (IL-6 and TNF-α) to stabilize liver function and improve organ damage.

The MARS system consists of an albumin-impermeable membrane separating the patient's blood from the albumin dialysate solution. The free albumin in the dialysate attracts and binds the liver toxins in the patient's blood. The albumin dialysate, in its turn, is regenerated by a low flux dialysis filter and two adsorber cartridges, one filled with activated charcoal, the other with an anion exchanger resin. The regenerated albumin solution is then ready for new uptake of toxins from the blood, entering the circuit through a high permeability filter to undergo standard dialysis to remove water-

soluble toxins.

Some studies have reported better survival rates in patients treated with MARS compared to conventional CRRT, but overall survival remains very poor (37% at 7 d and 25% at 30 d). The main factor affecting survival is the patient's clinical status before treatment[75,76].

In 2000, a trial by Mitzner *et al*[75] assessed survival rates in 13 patients with type I HRS. The eight patients treated with MARS had significantly better survival rates at 30 d than patients receiving standard medical therapy. By contrast, the randomized RELIEF study failed to show any significant differences in terms of survival in 189 patients treated with MARS *vs* standard medical therapy even though some benefit was noted in the management of encephalopathy in patients with type I HRS who underwent MARS[77].

After a one-year follow-up, Donati *et al*[78] reported that among 64 patients treated with MARS, the best survival rates were found in the 11 patients who subsequently underwent liver transplant. The same authors observed an improvement in both systolic and diastolic blood pressure in 5 patients with type 2 HRS treated with MARS and standard medical therapy.

Fractionated plasma separation and absorption (Prometheus)

The Prometheus system consists of a primary circuit (plasma filter and dialyzer) and a secondary circuit (adsorbent filters to remove bilirubin) for the combined removal of toxin albumin-bound and water-soluble molecules using a fractionated plasma separation and adsorption (FPSA) system. Unlike MARS, the plasma is separated from the blood through a high cut-off point polysulfone membrane (250 kDa, albumin permeable) and purified from the albumin-bound toxins by direct adsorption on resin-containing cartridges. The purified plasma is then returned to the blood circuit through a high efficiency dialyzer to remove water-soluble toxins.

The HELIOS study on 179 patients with liver failure treated with standard medical therapy *vs* extracorporeal treatment showed no significant advantage in terms of overall survival except in the subgroup of patients with type I HRS treated with FPSA who had a significant survival benefit[79].

Liver transplantation

Liver transplantation remains the treatment of choice in HRS patients despite its mortality rate which is particularly high in patients with type I HRS whose survival is so poor that many die while awaiting transplant.

Recovery of renal function is not universal: Marik *et al*[80], in a study on 28 patients, noted a complete recovery of kidney function in only 58% of transplanted patients, a partial recovery in 15% and no recovery in 25% (observation time 110 d). Renal sodium excretion, serum creatinine and neurohormonal levels may normalize within a month whereas renovascular resistance may take more than a year to return to normal after transplantation[81,82].

Organ allocation is mainly based on the MELD score, a system devised to stratify disease severity on the basis of laboratory parameters (serum creatinine, bilirubin and INR) to assign organs according to the so-called sickest first policy[83].

Considering all liver transplant recipients, those with HRS are more exposed to post-transplant complications, at greater risk of developing CKD and have a shorter overall survival[84,85]. Those patients who fail to recover renal function and need to continue hemodialysis have an even worse survival rate (70% mortality at one year)[86].

RRT prior to liver transplant is an important predictive factor. Patients undergoing hemodialysis for more than eight weeks have a markedly reduced probability of renal recovery and a combined liver-kidney transplant is recommended in these cases[87,88] .

Vasopressor treatment of HRS before liver transplant does not seem to affect subsequent patient outcome[89]. Nonetheless, Angeli *et al*[83] reported that liver transplantation may be delayed in patients treated with vasopressors following a response to treatment and hence an improvement in clinical and hemodynamic status. This paradoxical situation must be avoided and the clinical criteria adopted to establish the priority of patients on the waiting list for transplant (first and foremost the MELD score) must always refer to the patient's initial condition and not to the status reached after treatment.

There are no specific recommendations as to post-transplant immunosuppressive therapy, but it may be advisable to delay the start of cyclosporine or tacrolimus to 48-72 h after transplantation to enhance renal recovery as suggested by Guevara and Arroyo[90].

CONCLUSION

HRS is a life-threatening complication arising in patients with liver cirrhosis and triggered by a series of complex hemodynamic and neurohormonal changes linked to the liver disease. The condition carries a very poor prognosis and high morbidity and mortality rates.

Recent years have seen a reduction in HRS prevalence and an improvement in patient outcome probably reflecting a better understanding of HRS pathophysiology and advances in therapeutic strategies.

Treatment consists of medical management (mainly based on vasopressor administration), surgery (TIPS) or instrumental therapies (*e.g.,* renal replacement and liver support systems). Although the therapeutic armamentarium at our disposal will control the syndrome and obtain temporary remission, there is no guarantee of disease resolution.

The only effective treatment offering patients the hope of complete recovery is liver transplantation or combined kidney-liver transplant in selected cases. The decision to embark on transplantation must be carefully assessed in HRS patients considering all the potential

factors likely to influence transplant surgery and its outcome.

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When to initiate renal replacement therapy: The trend of dialysis initiation

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Abstract

The timing of renal replacement therapy for patients with end-stage renal disease has been subject to considerable variation. The United States Renal Data System shows an ascending trend of early dialysis initiation until 2010, at which point it decreased slightly for the following 2 years. In the 1990s, nephrologists believed that early initiation of dialysis could improve patient survival. Based on the Canadian-United States Peritoneal Dialysis study, the National Kidney Foundation Dialysis Outcomes Quality Initiative recommended that dialysis should be initiated early. Since 2001, several observational studies and 1 randomized controlled trial have found no beneficial effect when patients were placed on dialysis early. In contrast, they found that an increase in mortality was associated with early dialysis initiation. The most recent dialysis initiation guidelines recommend that dialysis should be initiated at an estimated glomerular filtration rate (eGFR) of greater than or equal to 6 mL/min per 1.73 m^2. Nevertheless, the decision to start dialysis is mainly based on a predefined eGFR value, and no convincing evidence has demonstrated that patients would benefit from early dialysis initiation as indicated by the eGFR. Even today, the optimal dialysis initiation time remains unknown. The decision of when to start dialysis should be based on careful clinical evaluation.

Key words: End-stage renal disease; Renal replacement therapy; Dialysis; Estimated glomerular filtration rate; Creatinine clearance; Survival

Core tip: In the United States, the number of patients who were placed on dialysis early increased dramatically from 1996 to 2010 and then decreased slightly. To investigate the proper timing of renal replacement therapy (RRT), we reviewed the literature and found that the results from different studies were conflicting, so that the optimal time of dialysis initiation remained unknown. Early initiation of RRT may contribute to the

current high incidence of RRT. If properly delayed RRT initiation is demonstrated to be safe for patients, this strategy may reduce the high incidence of RRT.

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INTRODUCTION

Over the past 2 decades, the numbers of patients with uremia and patients who have received renal replacement therapy (RRT) have increased worldwide. At the same time, the percentage of patients who initiated dialysis early increased dramatically from 1996 to 2010[1], which might have contributed to the high incidence of end-stage renal disease. RRT initiation can be intentionally delayed with careful monitoring. Delaying the initiation of RRT might be a strategy to reduce the incidence of RRT, if it is safe for patients. To investigate the effects of RRT timing on patient outcome, we conducted a literature review; we report its results in this paper.

RRT TRENDS

The early dialysis initiation trend

Twenty years ago, dialysis was not initiated until patients had life-threatening or severe symptoms of uremia. Emergency dialysis was needed for resistant hyperkalemia, with the emergence of metabolic acidosis. In 1995, Hakim *et al*[2] identified the indicators for RRT initiation: Patients with pericarditis, fluid overload, pulmonary edema, hypertension, advanced uremic encephalopathy, clinically significant coagulopathy, persistent and severe nausea and vomiting and who were poorly responsive to drug therapy should be placed on RRT immediately. If conservative non-dialysis management was ineffective for the following manifestations, the initiation of RRT was also suggested: (1) a general but fairly severe decline in quality of life (QOL), including vomiting, resistance and severe pruritus; and (2) decreased attentiveness, memory, cognitive abilities and depression that could affect the interpersonal relationships of the patient.

Hakim's standard was mainly based on clinical symptoms, and the timing of RRT initiation was apparently late. The point at which dialysis is initiated should be neither too late nor too early. If dialysis is started too late, patients risk the complication of uremia, which leads to low QOL and a higher risk of mortality. Dialysis is not a physiological process. As such, It (1) places the patient under the dangers of complications related to the RRT process; (2) accelerates the reduction of endogenous renal function[3], especially for elderly or frail patients with high rates of comorbidities; and (3) provokes or aggravates depression and other psychosocial problems. All of the above conditions correlate with an increased risk of mortality[4,5].

In the 1990s, the initiation of early dialysis was determined by the estimated glomerular filtration rate (eGFR), in accord with a Modification of diet in renal disease (MDRD) equation; the criterion was an eGFR greater than or equal to 10 mL/min per 1.73 m^2. Many researchers in the academy thought that early dialysis initiation would improve patient QOL and patient survival by reducing the complication of dystrophy. Furthermore, it was also believed that a decreased glomerular filtration rate GFR at dialysis initiation was associated with an increased probability of hospitalization and death[6-9]. They held the idea that early dialysis initiation was indispensable for preventing and reversing the deteriorated nutritional status associated with progressive uremia. The National Dialysis Cooperative Study[9] introduced the Kt/V_{urea} metric as a predictor of morbidity and mortality. Then, in 1996, the Canadian-US Peritoneal Dialysis (CANUSA) study[10] recommended a potential renal survival benefit of a weekly Kt/V_{urea} of greater than 2.0 [peritoneal creatinine clearance (CC) of > 70 L per 1.73 m^2]. This threshold is equivalent to a CC of 9-14 mL/min per 1.73 m^2. Based on the CANUSA study, the National Kidney Foundation Dialysis Outcomes Quality Initiative hemodialysis Adequacy Guideline (1997)[11] recommended that dialysis be initiated when the GFR decreased to 10.5 mL/min per 1.73 m^2 unless the normalized protein nitrogen appearance was more than 0.8 g/kg and the patient had a stable weight and a good appetite. Since then, the majority of national and international guidelines have promoted early dialysis for patients with deteriorating nutritional status and with symptoms or co-morbidities[12]. The Canadian Society of Nephrology (CSN) (1999)[13] suggested that dialysis be initiated when eGFR less than 12 mL/min per 1.73 m^2 in the presence of uremia symptoms or malnutrition. In the meantime, the indicator for dialysis initiation changed from the Kt/V_{urea} to the eGFR. The European Renal Best Practice (ERBP) (2002)[14] advocated for closer supervision of high-risk patients (those with eGFR < 15 mL/min per 1.73 m^2 plus symptoms and signs, the inability to control hydration status or blood pressure, and progressive nutritional status deterioration). High-risk patients, such as diabetics, may benefit from an earlier start. In 2006, the Kidney Dialysis Outcomes Quality Initiative (KDOQI)[15] updated these guidelines and suggested that RRT be considered when eGFR of < 15.0 mL/min per 1.73 m^2. Particular clinical considerations and certain characteristic complications may prompt the initiation of therapy before the onset of end-stage renal disease (ESRD). When the eGFR is greater than 15.0 mL per minute, RRT may also be warranted for patients with coexisting conditions such as diabetes or with symptoms of uremia.

All of the studies and guidelines mentioned above support early dialysis, and they have all been promoted

Table 1 Study and recommendations that support early dialysis initiation

Study/ recommendations	Year	Time/eGFR (mL/min per 1.73 m^2)	Journal
CANUSA study	1996	9 to 14	*J Am Soc Nephrol*
NECOSAD study	2001	No beneficial effect of earlier dialysis initiation	*Lancet*
NKF-DOQI	1997	10.5	*Am J Kidney Dis*
CSN	1999	< 12	*J Am Soc Nephrol*
KDOQI	2006	< 15.0	*Am J Kidney Dis*

eGFR: Estimated glomerular filtration rate.

as conventional wisdom (CW)[2,9,12]. The CW can be summarized as follows: (1) low levels of dialytic and endogenous renal clearance are associated with improved morbidity and mortality; (2) nutrition can be improved with the early initiation of dialysis; (3) dialysis should be initiated earlier in diabetics than in nondiabetics; and (4) dialysis initiated at eGFRs below 6 mL/min per 1.73 m^2 is potentially dangerous.

The trend toward early initiation of dialysis can also be seen internationally. According to the United States Renal Data System (USRDS)[1], with the eGFR calculated using the chronic kidney disease epidemiology calculation (CKD-EPI equation) (CKD-EPI eGFR, mL/min per 1.73 m^2), the percentage of ESRD patients who started RRT at higher eGFR levels increased steadily from 1996 until 2010. In 1996, 9.48% of patients initiated RRT with an eGFR of 10-14.9 mL/min per 1.73 m^2, and only 3.01% had an eGFR > 15 mL/min per 1.73 m^2. In 2010, these percentages had more than doubled (to 27.85% and 14.71%, respectively). This phenomenon was more prominent in the elderly dialysis population. The percentage of incident ESRD patients who started dialysis at an eGFR < 5 mL/min per 1.73 m^2 decreased from 34.4% in 1996 to 12.6% in 2010[1]. In Beijing, the percentage of patients who initiated hemodialysis with an eGFR > 10 mL/min per 1.73 m^2 rose gradually from 13.2% to 20.7% between 2007 and 2010[16]. In Europe[17], dialysis initiation when eGFR > 10.5 mL/min per 1.73 m^2 had risen from 16.4% to 23.6% between 1999 and 2003. The United Kingdom Renal Registry data[18] showed that, between 1997 and 2010, the mean eGFR at dialysis initiation increased from 6.2 to 8.7 mL/min per 1.73 m^2. In data from the Canadian Organ Replacement Registry[19], the percentage of patients who started peritoneal dialysis at an eGFR > 10.5 mL/min per 1.73 m^2 rose from 29% (95%CI: 26%-32%) to 44% (95%CI: 41%-47%) between 2001 and 2009. The average eGFR at dialysis initiation increased from 9.3 ± 4.6 to 10.7 ± 6.1 mL/min per 1.73 m^2 (Figure 1 and Table 1).

Studies and recommendations that support late dialysis initiation

Recently, certain registry and observational studies that included a total of > 900000 analyzable patients all demonstrated that late dialysis initiation was associated with improved survival[14,20].

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)[21] showed that, though not significant (adjusted HR = 1.66; 95%CI: 0.95-2.89), the early group (which was initiated according to the first KDOQI guidelines) gained an estimated survival benefit of 2.5 mo *vs* late starters after 3 years of dialysis. In the NECOSAD study, the eGFR was calculated from timed urine collections (as the mean of urea and CC). However, there was a delay of at least 4.1 mo before dialysis initiation in the late-start group[21]. After taking the lead time bias (discussed below) into account, there was no beneficial effect of earlier dialysis initiation. In 2002, Traynor *et al*[22] also found that there was no significant survival benefit from earlier initiation of dialysis and that patients who started dialysis with a lower estimated CC survived longer. More recent observational data[17,23-34] found a comorbidity-adjusted survival disadvantage for early dialysis initiation, as 12 studies found an increase in mortality associated with early dialysis initiation. Beddhu *et al*[23] found that for each 5 mL/min increase of the MDRD eGFR, the associated risk of death was 27% higher (HR = 1.27; $P < 0.001$). However, this phenomenon was not observed for the CC value. In a Chinese study in Taiwan[29], the median eGFR level at dialysis initiation was 4.7 mL/min per 1.73 m^2 from July 2001 to December 2004 in > 23000 incident patients. Based on the eGFR level at dialysis initiation, patients were divided into quintiles, and the best survival was observed at < 3.29 mL/min per 1.73 m^2. In another report, the best survival was achieved in patients with eGFRs of between 0 and 5 mL/min per 1.73 m^2[27] among American subjects. This study included 81176 uremic subjects, aged 20-64 with no substantial comorbidities other than hypertension, from the USRDS dataset[27]. In 2012, Yamagata *et al*[31] analyzed 20854 patients who had started RRT in 1989 and 1990 and found that the timing of RRT initiation had no impact on the long-term prognosis after adjustments were made for co-morbid conditions. In 2014, Crews *et al*[33] found that, compared with patients who started at a lower eGFR, patients with early dialysis initiation at an eGFR ⩾ 10 mL/min per 1.73 m^2 showed greater mortality and more frequent hospitalization, even after adjusting for comorbid conditions. In 2014, a study of 310932 patients who had started dialysis between 2006 and 2008[32] demonstrated that no harm or benefit was associated with early dialysis initiation. A meta-analysis of cohort studies and trials by Susantitaphong *et al*[34] found that a 1 mL/min per 1.73 m^2 increase in the GFR at dialysis initiation was associated with 3%-4% higher all-cause mortality after adjustment for comorbid conditions.

Possible explanations for the conflicting results

Previous studies provide reproducible evidence that dialysis initiation with higher eGFR is associated with increased mortality. However, these studies also have

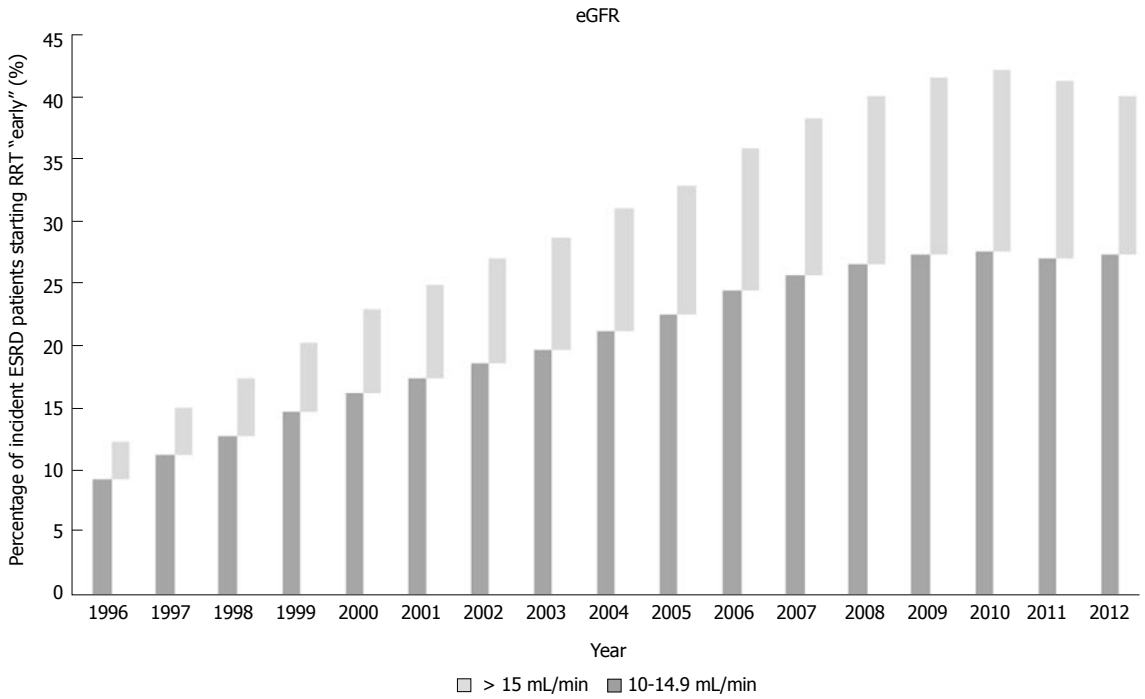

Figure 1 Percentage of patients initiating renal replacement therapy "early" in the United States during the years 1996-2012. Data from the United states Renal Data system. eGFR calculated using the CKD-EPI equation [CKD-EPI eGFR (mL/min per 1.73 m^2)]. ESRD: End-stage renal disease; eGFR: Estimated glomerular filtration rate.

shortcomings. The limitations of the prior studies are discussed below.

Inaccurate eGFR values

The decision to initiate RRT has relied heavily on the eGFR[12]. The ERBP[23] concluded that creatinine-based measures of the eGFR in pre-dialysis patients were fundamentally flawed and were thus invalid. In studies using GFR measures that were based on 24-h urine urea and/or creatinine clearance, the adverse effect of early initiation was not found. The MDRD equation accounts for the average loss of muscle over time with age (sarcopenia) but does not account for unusual body habitus or diet. In other words, the MDRD equation may be erroneous for patients with ESRD. Craig *et al*[35] concluded that, when compared with the reference standard radionuclide GFR (rGFR), the MDRD equations performed poorly in patients with advanced renal failure, while the Cockcroft-Gault (CG) equation showed a smaller bias and was more accurate. In this study, an intravenous injection of 51Cr-EDTA (3 MBq) was used for the measurement of rGFR, and plasma samples were taken approximately 120 and 240 min later. The study recommended using the CG equation when the rGFR method is unavailable. It must be kept in mind that the differences between the GFR methods may greatly influence the decision for RRT initiation[36].

There are possible explanations for falsely over-estimated eGFR. First, patients with low muscle mass due to inactivity or malnutrition have a lower creatinine generation rate, which would overestimate the true residual renal function (RKF). Second, fluid overload would dilute patient serum creatinine levels. All such patients would have higher co-morbidity rates and lower serum creatinine levels. The serum creatinine-based eGFR might overestimate the true GFR in the above patients and thus risk including such patients in the "earlier" start groups[14] when they should in fact start late.

Elderly or frail patients were more likely to start dialysis early

Patients with symptoms or co-morbidities were more likely to be started on dialysis early. The multivariate adjustment for co-morbidities indeed decreased the benefit of initiating dialysis with a low eGFR, but the effects did not disappear. The most common reason to initiate dialysis early was a nutritional decline. Compared with nondiabetic dialysis patients, the association of an early start with higher mortality was much stronger among patients with diabetes[26]. It was confirmed that patients with low comorbidity burdens showed reduced survival compared to higher starting eGFR values[17,22-27,29].

Lead time bias

Unfortunately, the studies that support early dialysis initiation fail to take the effect of the lead time bias into consideration. The lead time bias is related to the initiation time of treatment within the duration of the disease. The prolonged survival may be due merely to earlier diagnosis and treatment. Alternatively, it may be expected that earlier disease detection would be correlated with longer survival. After eliminating the

effect of the lead time bias, the NECOSAD study[21] demonstrated that there was no beneficial effect of earlier dialysis initiation.

High-risk patients may die before dialysis initiation in the late group

Some studies only included patients who actually started dialysis. Those who died before dialysis had been initiated (possibly because of uremia) were excluded. In other words, the late-start subjects may not suffer from severe disease who died before the initiation of dialysis. Only the fittest patients who survived long enough were included in the late-start groups.

Treatment time on RRT

Mortality might be a result of "insufficient" dialysis. Long treatment times (> 4 h per session) and more frequent dialysis sessions reduced the risk of low albumin, which is correlated with decreased mortality[37,38].

Cardiovascular comorbidities and infection

Early-dialysis patients were more likely to die in the hospital. Compared with patients who underwent conservative management, patients who underwent dialysis expected longer days in the hospital and were more likely to die in the hospital, especially when debilitated, frail, or elderly[39]. In the first year of hemodialysis, deaths were mainly due to cardiovascular disease and infection[1]. The all-cause mortality, cardiovascular disease mortality, and mortality due to other causes peaked in month 2 and then decreased thereafter[13]. Dialyzed patients had twice the rate of sudden death, which was connected with ultrafiltration volumes, decreased blood pressure, lower Kt/V_{urea}, and low potassium concentrations[40]. Cardiovascular disadvantages can also appear when accompanied with life-threatening diseases such as pulmonary edema. The risk of infection was associated with the modality and access type. In a study of 55 inpatients who underwent tunneled hemodialysis catheter (TDC) removals, 36.4% had proven bacteremia, 41.8% had a fever and 20% had clinical signs of sepsis with hemodynamic instability or respiratory failure[41]. The risk of TDC is thus apparent. Once a patient has started dialysis, the risks of all forms of infection are much higher, and the patient is more likely to have septicemia, which is especially prevalent among elderly patients.

The IDEAL study

The randomized controlled trial of early *vs* late initiation of dialysis (IDEAL) study[42] showed no difference in mortality between the early and late groups. The early group was expected to start dialysis when the CC (calculated with the CG equation) was 10-14 mL/min per 1.73 m^2, and the late group was expected to start dialysis at 5-7 mL/min per 1.73 m^2. It was allowed to start dialysis based on clinical indications, disregardfulness CC in either group. The average CC values were 12.0 and 9.8 mL/min per 1.73 m^2 at the time of dialysis initiation in the early and late groups, respectively. Compared with the early group, the late group showed a 6-mo delay in initiation. However, 76% of the patients who were allocated to the late group actually commenced dialysis with a higher CC, and the mean difference in the estimated GFR between the late and early groups was only 2.2 mL/min. The gap between the 2 groups was too small to generate a difference in the mortality rates. However, for some patients, who started RRT after their eGFR values dropped below 5-7 mL/min per 1.73 m^2, no harm was detected. In other words, initiating dialysis late might be safe for some patients with fluid overload or other accompanying complications if they are carefully monitored.

Recommendations that support late dialysis

Notably, most patients are symptomatic and need to be dialyzed in a GFR range of 6-9 mL/min per 1.73 m^2. Many guidelines, including the ERBP 2002[14], the Australia 2005[43] and the United Kingdom 2009[44], recommend that RRT should be initiated before the GFR reaches 6 mL/min per 1.73 m^2. The ERBP 2002[14] recommends that dialysis preparation should be initiated at a GFR of 8 mL/min per 1.73 m^2 and that dialysis must be initiated at a GFR of 6 mL/min per 1.73 m^2. Caring for Australians with Renal Impairment (2005)[43] recommends that dialysis should be initiated when the GFR is less than 10 mL/min per 1.73 m^2 if symptoms of uremia or complications such as malnutrition are present or when the GFR is less than 6 mL/min per 1.73 m^2 in the absence of symptoms or complications. The United Kingdom Renal Association 2009[44] recommends RRT initiation when the eGFR is less than 6 mL/min per 1.73 m^2, even if the patient is asymptomatic. The 2012 Kidney Disease Improving Global Outcomes[45] suggests that dialysis should be initiated when the eGFR is approximately 5-9 mL/min per 1.73 m^2. The CSN 2014 clinical practice guidelines[46] suggest that chronic dialysis should be initiated when the eGFR drops to 6 mL/min per 1.73 m^2, even if there are no clinical indications. However, the existing guidelines do not specify a dialysis initiation point (with respect to eGFR or serum creatinine level). In the USRDS[1], the percentage of incident ESRD patients who began RRT at higher eGFR levels decreased slightly in 2011 and again in 2012. The percentage of patients who began RRT at an eGFR $\geqslant$ 10 mL/min per 1.73 m^2 decreased from 42.6% in 2010 to 40.5% in 2012, and the percentage of patients who initiated RRT at an eGFR < 5 mL/min per 1.73 m^2 rose from 12.6% in 2010 to 13.7% in 2012 (Table 2).

CONCLUSION

There is still considerable doubt with respect to the optimal timing of dialysis initiation in uremic populations. The timing of dialysis is often affected by multiple factors, including age, diabetes mellitus, individual desire, socioeconomic status, personal beliefs, and

Table 2 Study and recommendations that support late dialysis initiation

Ref./ recommendations	Year	Time/eGFR (mL/min per 1.73 m^2)	Journal
Beddhu *et al*[23]	2003	5-mL/min increase of the associated risk of death was 27% higher	*J Am Soc Nephrol*
Chinese Taiwan study	2010	< 3.29	*Nephrol Dial Transplant*
Rosansky *et al*[27]	2011	Between 0 to 5	*Arch Intern Med*
Yamagata *et al*[31]	2012	No difference	*Ther Apher Dial*
Crews *et al*[33]	2014	< 10	*J Am Soc Nephrol*
Susantitaphong *et al*[34]	2014	1 mL increase 3%-4% higher all-cause mortality	*Am J Kidney Dis*
Scialla *et al*[32]	2014	No difference	*Kidney Int*
ERBP	2002	8, and to be sure at 6	*Nephrol Dial Transplant*
Australia	2005	Evidenced symptoms or complications: < 10, no symptoms or complications < 6	
United Kingdom	2009	< 6	
K/DIGO	2012	5-9	
CSN	2014	< 6	*CMAJ*

eGFR: Estimated glomerular filtration rate.

the patient's cultural and educational background. Initiating dialysis early based solely on a single objective measurement (specific level of GFR) can be harmful. Most patients begin dialysis because of renal failure-related symptoms. Importantly, dialysis therapy is not innocuous, and it does not replace all the functions of the kidney. Compared with patients who received dialysis, the native Kt/V_{urea} of an able-bodied man is more than 15-fold higher. Some scholars believe that the biggest advantage of dialysis is the alleviation of fluid overload. Thus far, we lack validated and objective measures of the uremic state that could be used to guide the timing of dialysis initiation. Currently, the established guidelines for the timing of dialysis are based on the conclusions of many observational studies. Data from randomized controlled trials that establish optimal timing for RRT are lacking. The time at which dialysis is initiated must be individualized, and further studies are required to explore a comprehensive, systematic dialysis index that is associated with the GFR, with symptoms, and with assumed indications for dialysis initiation.

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CASE REPORT

Lupus-associated thrombotic thrombocytopenic purpura-like microangiopathy

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Author contributions: Blum D performed the chart review of the case being described, searched, reviewed and critically appraised the literature for cases of thrombotic microangiopathy in patients with lupus; Blake G was involved in making the presumptive diagnosis of the TTP-like syndrome in the patient with lupus described in this case report, and in initiating the management of this rare complication of lupus; Blake G also reviewed and amended this case report manuscript prior to its submission.

Institutional review board statement: Not applicable; this report describes the clinical course of a patient under the care of the general medicine team at the Montreal General Hospital.

Informed consent statement: Explicit written informed consent was obtained from the patient described in this case prior to submitting this case report. A copy of the consent form signed by this patient can be provided upon request.

Conflict-of-interest statement: The authors have no conflicts of interest to report.

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Abstract

Recently reported cases of lupus complicated by a thrombotic thrombocytopenic purpura (TTP)-like syndrome suggest a survival benefit to early treatment with plasma exchange. The following is a report of the eighth such case in the last ten years. A 44-year-old lady known for lupus presented with the nephrotic syndrome and a renal biopsy was consistent with class 4G lupus nephritis. She was given high-dose steroids and cytotoxic therapy, but her induction therapy was complicated by the classic pentad of TTP. She was subsequently treated with another course of high-dose steroids, a different cytotoxic agent, and plasma exchange, with clinical resolution shortly thereafter. Similar to seven recently reported cases of microangiopathy in lupus, this lady's TTP-like syndrome improved dramatically after initiation of plasma exchange, despite not having a severely deficient ADAMTS13. This has implications on both current clinical practice and on the pathogenesis of TTP-like syndromes in lupus.

Key words: Microangiopathic hemolytic anemia; Microangiopathy; Thrombotic thrombocytopenic purpura; Atypical hemolytic-uremic syndrome; Hemolytic uremic syndrome; Systemic lupus erythematosus associated thrombotic thrombocytopenic purpura-like microangiopathic hemolytic anemia; Lupus nephritis; Lupus; Plasma exchange

Core tip: In patients with lupus who develop thrombotic microangiopathy, early initiation of plasma exchange appears to carry a survival benefit - even in those patients whose ADAMTS13 activity levels are not severely deficient. This improved survival has become apparent in the last ten years during which time seven cases of thrombotic microangiopathy complicating lupus and treated with plasma exchange have been reported. The present article describes the eighth such case, reviews the previously described cases and outcomes of microangiopathy in lupus, and hypothesizes as to why plasma exchange appears to be beneficial in this subset of patients with atypical haemolytic uremic syndrome.

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INTRODUCTION

Microangiopathic hemolytic anemia (MAHA) is caused by a number of conditions, several of which are fatal. One such condition is thrombotic thrombocytopenic purpura (TTP), which has been reported to be less responsive to therapy in patients with lupus as compared to the general population[1]. Recent research has revealed a subset of patients with lupus who have a TTP-like syndrome distinct from TTP[2]. We report a case of a patient with lupus and a TTP-like syndrome who received early plasma exchange and survived. A review of this under-recognized clinical entity follows.

CASE REPORT

A 44-year-old lady with a five-year history of systemic lupus erythematosus (SLE) on hydroxychloroquine presented to the Montreal General Hospital with edema, nausea, and vomiting in January 2014. On exam she was noted to have anasarca and hypertension. She was found to have a creatinine of 335 μmol/L and a urea of 54 mmol/L (normal 2-10 mmol/L). Her serum albumin was low and her urine tested positive for protein. Her urine sediment revealed white cell casts, red cells, and oval fat bodies. She was diagnosed with new-onset nephrotic syndrome. Further workup was consistent with a lupus flare with an anti-dsDNA > 800 (negative < 20), and excluded alternative causes such as ANCA-related vasculitides, hepatitis C, and human immunodeficiency virus. She had a renal biopsy which was consistent with lupus nephritis class Ⅳ-G with a predominance of active lesions and 75% cellular crescents; there was no thrombotic microangiopathy.

She was treated with a 3-d pulse of higher dose steroids followed by daily steroid doses equivalent to 1 mg/kg of prednisone. She was started on mycophenolate. Her in-hospital course was marked by persistent vomiting requiring prolonged admission.

Ten days after presentation she was noted to have a falling platelet number and falling hemoglobin. Twelve days after presentation, her hemoglobin fell to a nadir of 39 g/L (from 83 g/L on presentation) (normal 120-150 g/L), requiring transfusion of 2 units of pRBC, and her platelets fell to a nadir of 70 × 10^9/L (from 330 × 10^9/L on presentation) (normal 150-450 × 10^9/L). Her white count was normal. She had no evidence of bleeding, fibrinogen of 5.2 g/L (normal > 1.5 g/L), and normal PT, aPTT. She did not have anti-cardiolipin antibodies. Her reticulocytes were 48. Her Coombs test was weakly positive for IgG. Her LDH was slightly elevated at 246 U/L (normal < 220 U/L), her total bilirubin was 12.5 mmol/L (normal < 20 μmol/L), her haptoglobin was decreased at 0.66 g/L, and several blood smears consistently showed a 10%-15% fragmentation index (normal < 0.5%) in addition to rouleaux formation. There was no bloody diarrhea. Her creatinine was higher than it was at presentation, peaking at 417 mmol/L on the same day as the hemoglobin nadir. Shortly thereafter she became acutely hypoxemic from volume overload refractory to diuretics, and required ultrafiltration. She then became drowsy, and neurological exam was significant for increased reflexes bilaterally.

TTP could not be excluded; therefore she was treated with five days of plasma exchange with fresh frozen plasma (FFP), followed by plasma exchange every second day. She was given a second course of pulse steroids, cyclophosphamide was started, and mycophenolate was stopped. She was also given a dose of intravenous iron sucrose and was started on erythropoietin given the inappropriately normal reticulocyte count.

Following a course of eight plasma exchanges, her platelet count recovered completely to > 200 × 10^9/L, her fragmentation index decreased to below 1%, and her hemoglobin stabilized around 75 g/L. Her cell counts stabilized off of plasma exchange. She remains on prednisone and cyclophosphamide. She now responds to diuresis, and her markers of active inflammation have all reduced. Her anti-dsDNA was 50 in February 2014. Ultimately her ADAMTS13 activity, which was measured prior to initiation of plasma exchange, returned at 49%. This level is only slightly below the lower limit of 56% and therefore both excludes the diagnosis of TTP and is consistent with the diagnosis of an SLE-associated TTP-like MAHA.

DISCUSSION

MAHAs are characterized by intravascular hemolysis. The usual laboratory findings are normocytic anemia, thrombocytopenia, elevated LDH, reduced haptoglobin, and elevated unconjugated bilirubin. The peripheral

Table 1 Differential diagnosis of microangiopathic hemolytic anemia

Disseminated intravascular coagulation
Thrombotic thrombocytopenic purpura
Hemolytic uremic syndrome
Atypical hemolytic-uremic syndrome
[1]TTP-like MAHA, an aHUS presenting as part of a connective tissue disease
[1]Anti-phospholipid syndrome
Hemolysis with elevated liver enzymes and low platelets of pregnancy
[1]Malignant hypertension
Medications
Malignancy
Mechanical cardiac valves or other foreign bodies in the circulatory system

[1]Indicates conditions at which patients with lupus are at higher risk compared to the general population. TTP: Thrombotic thrombocytopenic purpura; aHUS: Atypical hemolytic-uremic syndrome.

blood smear classically shows schistocytes, or fragmented red cells, which are required to make the diagnosis. The differential diagnosis of MAHA is limited to only a few conditions (Table 1). Patients with lupus are at particular risk for acquiring the anti-phospholipid syndrome, malignant hypertension, and SLE-associated TTP-like MAHA. As its name suggests, SLE-associated TTP-like MAHA is a condition manifested by otherwise unexplained MAHA in a patient meeting the American College of Rheumatology (ACR) criteria for systemic lupus; this condition may be associated with the other classic findings of TTP including acute renal failure, fever, and neurological deterioration, but is not associated with a severe reduction in ADAMTS13 activity, nor is it associated with diarrhea. TTP itself is defined by a MAHA where the activity level of ADAMTS13 is severely deficient. TTP-like MAHAs that occur simultaneously with connective tissue diseases are rare but clinically relevant illnesses that are becoming increasingly recognized as a distinct subgroup of atypical hemolytic uremic syndrome.

Over the last 60 years there have been 127 reported cases of MAHA resembling TTP occurring in patients with SLE. A 2003 review of the English literature from 1968 to 2002 had identified 56 such cases and had suggested that TTP in patients with SLE was associated with a higher mortality than idiopathic TTP, even with optimal treatment[1]. However, the vast majority of the patients in that review were treated prior to the advent of plasma exchange as the optimal therapy for TTP; instead these patients were generally treated with multiple modalities including plasmapheresis without exchange.

In the last ten years, there have been seven additional reported cases of purported TTP occurring in patients meeting the ACR criteria for SLE. Six of these patients were treated with plasma exchange in a timely manner, with or without steroids or cytotoxic therapy, and survived[3,4]. One patient did not receive plasma exchange promptly upon diagnosis and died in hospital[5].

A retrospective study from Japan in 2009 that reviewed a university hospital database for cases of thrombotic microangiopathy occurring in patients with connective tissue disease identified an additional sixty-four patients with thrombotic microangiopathy and SLE. Forty-five of these sixty-four patients received plasma exchange, with or without steroid therapy. Eighteen of the sixty-four died, although the reported data did not clearly address if there was a higher risk of death in patients who were not treated with plasma exchange[2].

Including the case reported here, there are now at least eight cases over the last ten years that suggest that early initiation of plasma exchange, with or without additional therapy, has the potential to be curative for TTP-like MAHA in patients with SLE.

Interestingly, the aforementioned Japanese study found that more than three quarters of the cases of thrombotic microangiopathy occurring in SLE were associated with normal or near normal ADAMTS13 activity. This suggests a different pathogenetic mechanism than that which occurs in idiopathic TTP[2,6], which is classically associated with a severely reduced ADAMTS13 activity. There is no consensus on the mechanism of TTP-like MAHA in lupus patients, but there are several hypotheses that are being investigated. These hypotheses implicate abnormal endothelial activation, elevated d-Dimers, ADAMTS13-resistant von Willebrand Factor, and defects in regulation of the complement system as culprits in causing the illness[6]. We did not measure a d-Dimer in our patient. She did have low C3 and C4 levels, 0.56 and 0.11 respectively, but these are expected given her active lupus. Investigations for mutations in genes encoding complement regulators were not sent. The other hypotheses mentioned could not be tested or confirmed easily in the clinical setting.

Returning to the 2003 review of 56 cases of TTP-like MAHA, an important observation is that plasma exchange appears to be associated with better outcomes than plasmapheresis without FFP infusion in lupus patients with a TTP-like syndrome. This implies that there may be a property of FFP that contributes to the reversal of the underlying pathogenetic process.

COMMENTS

Case characteristics

This 44-year-old lady known for lupus presented with the nephrotic syndrome, was found to have lupus nephritis, and her course of induction therapy was complicated by microangiopathic hemolytic anemia (MAHA), fever, rising creatinine with volume overload, and altered mental status.

Clinical diagnosis

The constellation of finings was suggestive of thrombotic thrombocytopenic purpura (TTP) complicating lupus nephritis.

Differential diagnosis

Atypical hemolytic-uremic syndrome (including a TTP-like syndrome occurring

in the context of a connective tissue disease), disseminated intravascular coagulation, antiphospholipid syndrome.

Laboratory diagnosis

In the context of intravascular hemolysis with schistocytes, rising creatinine, normal coagulation parameters, the absence of antiphospholipids, and an ADAMTS13 level that was not severely deficient, the most likely diagnosis is a TTP-like syndrome occurring in the context of lupus.

Imaging diagnosis

Chest radiography revealed pulmonary edema.

Pathological diagnosis

Histologic examination of the renal biopsy done on presentation revealed class 4G lupus nephritis without evidence of thrombotic microangiopathy; there was no repeat biopsy when she developed the constellation of features described above ten days after her induction therapy. Review of blood films taken after she developed the TTP-like clinical syndrome revealed elevated schistocytes.

Treatment

This lady was initially treated with a pulse of intravenous solumedrol and mycophenolate mofetil (MMF) for induction therapy for class 4 lupus nephritis; when she developed the constellation of features described above ten days later, she was given a second course of pulse IV solumedrol, cyclophosphamide instead of MMF, and plasma exchange.

Related reports

There have been over 50 reported cases of TTP-like syndromes occurring in patients with lupus in the literature, but only 7 such cases have been reported in the last ten years during which time plasma exchange has been the standard of care. Taking the most recent 7 cases as a case series, 6 were treated early with plasma exchange and survived while 1 did not receive plasma exchange early and died. Additionally, retrospective data from Japan has identified a subset of patients with microangiopathy complicating lupus who have near-normal ADAMTS13 levels. The implication is that in these patients, plasma exchange may have a survival benefit even in the absence of a severely deficient ADAMTS13, as suggested by the outcomes of the most recent case series.

Term explanation

MAHA: Characterized by elevated LDH, total bilirubin, decreased haptoglobin, and fragmented cells and schistocytes on blood film; TTP: A thrombotic microangiopathy manifested by fever, acute kidney injury, altered mental status, and intravascular hemolysis. Characterized by a severely deficient ADAMTS13 activity level; Atypical hemolytic-uremic syndrome (HUS): A thrombotic microangiopathy variably associated with acute kidney injury and intravascular hemolysis but with ADAMTS13 activity levels above the severely deficient range. It is often, but not always, associated with gene defects involving inhibitors of the alternative complement cascade; Lupus related TTP-like MAHA: A thrombotic microangiopathy syndrome similar to TTP but with near-normal ADAMTS13 activity; it is a subset of atypical HUS that occurs in patients with lupus and its etiology is unknown.

Experiences and lessons

TTP-like syndromes may complicate the course of active lupus and appear to respond favorably to treatments involving early plasma exchange despite being characterized by near-normal ADAMTS13 activity levels.

Peer-review

This is a very interesting clinical case of a rare complication of patients with LES.

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