An Overview about Acute kidney injury and chronic liver disease

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Abstract

Liver cirrhosis is defined as formation of regenerating nodules surrounded by fibrous bands due to chronic liver injury that ends up by liver cell failure and portal hypertension. unlike other complication of liver cirrhosis ,hepatic encephalopathy affect the quality of life of the patient and their family , for the patient frequent readmission and worsening the cognitive performance with each episode and increase dependency on the others. Acute kidney injury is defined as sudden loss of excretory function of Kidney, (AKI) is a part of disorders summarized as (AKD) acute kidney disease , in which slow deterioration of kidney function associated with permanent loss of kidney cells and nephrons which can lead to chronic kidney disease (CKD). Acute kidney injury is a common complication associated with liver disease especially decompensated liver disease , and the most common types of AKI occur with liver cirrhosis is the pre renal type and acute tubular necrosis . the pre renal type is more benign and respond to good fluid replacement but the renal type have a bad prognosis and require more specific treatment. Renal dysfunction in patient with chronic liver disease has been called hepato renal syndrome which result from wide spectrum of complication mainly portal hypertension that affect systemic hemodynamics then bile acid nephropathy, coagulopathy-induced bleeding from ischemic Acute tubular necrosis , related glomerular diseases (e.g., immunoglobulin, a nephropathy, hepatitis B and hepatitis C-related glomerulonephritis, cryoglobulinemia, membranoproliferative glomerulonephritis), and other comorbid diseases such as inherited cystic diseases.

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Acute kidney injury is defined as sudden loss of excretory function of Kidney, (AKI) is a part of disorders summarised as (AKD) acute kidney disease , in which slow deterioration of kidney function associated with permanent loss of kidney cells and nephrons which can lead to chronic kidney disease (CKD) . In(AKI) there is decrease in urine output and increase in serum Creatinine in a duration of 7 days and AKD can range from mild and self limited to sever and persistent ,some times occurs without meeting the criteria of rapid onset of (AKI) when(AKI)occurs slowly or doesn't resolve and in case persistent structural damage to kidney, if AKI persist >3 months it becomes CKD ***(1)***.

	AKI	AKD	CKD	NKD
duration	<7 days	<3 months	>3 months	NA
Functional criteria	Increase in sCr by ≥50% within 7 days or increase in sCr by ≥0.3 mg/dl (26.5 µmol/l) within 2 days or oliguria for ≥6 hours	AKI or GFR <60 ml/min/1.73 m^2 or decrease in GFR by ≥35% over baseline or increase in sCr by >50% over baseline	GFR < 60 ml/min/1.73 m^2	GFR ≥ 60 ml/min /1.73 m^2, stable GFR (no decrease by 35% within 3 months), stable sCr (no increase by 50% within 3 months or increase by 0.3 mg/dl within 2 days), no oliguria for ≥6 hours
And /or	OR	OR	OR	And
Structural criteria	Not defined	Elevated marker of kidney damage (albuminuria, haematuria or pyuria are most common)	Elevated marker of kidney damage (albuminuria is most common)	No marker of kidney damage

*NKD implies no functional or structural criteria according to the definitions for AKI, AKD or CKD. In patient with liver disease ,ascites and advanced cirrhosis ; renal impairment was first described by Hecker and Sherlok in 1960_s as hepato renal syndrome which refer to a syndrome result from systemic hemodynamic effects of advanced portal hyper tension**.** However we should keep in mind that renal function in patient with liver disease can be affected also by other complications as bile nephropathy, coagulopathy –induced bleeding from ischemic tubular necrosis , glomerular disease as hepatitis B and hepatitis C related glomerulonephritis and comorbid disease as inherited cystic disease AKI in patients with cirrhosis is associated with a 7-fold increase in morbidity and mortality vs those without AKI**.** Repeated episodes of AKI increase the risk of progression to chronic kidney disease (CKD)***(2)***

Mechanism of AKI ;

kidney physiology and kidney life span; The kidneys maintain homeostasis of body fluids, electrolytes, osmolality and pH, excrete metabolic waste products and secrete hormones . ***(3)***

As AKI cause disturbance in homeostasis, severe AKI is life threatening condition but kidney replacement therapy can maintains homeostasis until improvement of kidney function but in case of AKI in multi organ failure its lethal even if kidney replacement therapy occurs . ***(3)*** the nephron is the functional unit of kidney composed of glomerular and tubular part , the glomerular part has filtrating function of the fluid and small molecules and the tubular part reabsorbs most filtered molecules and secretes metabolic waste products, concentrating the urine to 1– 2 litres per day , the number of nephron decrease with age starting from the age of 25 year ***(4).***

Although the metabolic activity decline also with the age but the heathy individual do well with only half of the nephron without adaptation ***(4)*** but decrease number of nephrons beyond this number shorten the life span of kidney so incidence of CKD and kidney failure in elderly require increasing in kidney replacement therapy so AKI is an important risk factor of CKD . **pathophysiology of kidney failure;**

Fluid haemostasis is affected as decrease in GFR lead to activation of renin angiotensin system enhance fluid retention which appears in form of peripheral edema ,third space effusions and pulmonary congestion

specifically in heart failure . ***((5).***in addition electrolyte disturbance in form of hyperkalaemia as urinary excretion help to get rid of k , hyper or hyponatremia when the kidney loss the ability of urine concentration or dilution according to need , hyper phosphatemia in case of impairment phosphate clearance . ***(1)***.

Acid –base balance is also affected , in patient with AKI decreasing in capacity of excretion of fixed acid causing metabolic acidosis and respiratory compensation through increasing ventilatory drive widening of the anion gap caused by accumulation of phosphate , sulphate and small organic anions . decrease in excretion of metabolic waste products indicated by azotaemia but not only waste products as AKI cause disturbance in other metabolites haemostasis which all together responsible for symptoms of uraemia, such as fatigue, tremor or confusion ***(1)***.

Kidney failure affect most of the organs The lungs are affected by hyperpnoea to compensate for metabolic acidosis, hypervolaemia, cytokines, oxidative stress and cytotoxic elements of necrotic cell debris (released by parenchymal necrosis in the kidneys, causing microvascular injury, and eventually acute respiratory distress syndrome). AKI affects cardiac system via acidosis, hyperkalaemia, uraemic toxins, hypervolaemia, hypertension, and systemic inflammation. Uraemic encephalopathy also can occurs ***(6)***

kidney injury and recovery ;

reversible hypoperfusion of kidney that result in transient reduce GFR due to Volume depletion, haemorrhagic shock, and heart failure with reduced ejection fraction, hepatorenal syndrome ,venous congestion or hypercalcaemia, but if ischaemia persists may cause tubule necrosis**,** nephrotoxic drugs and contrast enhanced radiology can cause acquired AKI**.** Nephrotoxic drugs classified into main 6 categories ; chemotherapy as cisplatin and antimicrobials as amphotericin or aminoglycosides have direct nephrotoxic effect . Drugs that are cleared via the kidneys, such as vancomycin, because drug-induced kidney injury can lead to accumulation of the drug and its metabolites, further amplifying the toxicity ***(7).***

Second, some drugs cause nephrotoxicity via immune-mediated mechanisms, leading to allergic tubulointerstitial nephritis. Third , drugs as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, can cause a decrease in GFR by affecting intrarenal haemodynamic hypoperfusion of the kidney has dual effect either protect the nephron from hyperfiltration related progression to CKD or ischemic acute tubular necrosis ***(8).***

Fourth, drug metabolites crystallize inside the kidney tubules, causing intrarenal obstruction of urinary flow.

Fifth, failure intrarenal haemorrhage associated with oral anticoagulants. Lastly , the renal excretion of some drugs or drug metabolites competes with creatinine at the same tubular transporter . number of the lost nephrons irreversible in an AKI episode determine the prognosis of kidney function on long term . recovery of the kidney doesn't mean regeneration all the time as functional capacity will be augmented in an unaffected nephrons (compensatory hypertrophy). this adaptation can ensure short term survival but there is variable outcome on long term after AKI episode ***(9)***

Incidence ;

AKI related mortality exceed that of breast cancer , heart failure and diabetes. AKI is either hospital acquired which usually in high income countries or community acquired which usually in low income countries in high income countries AKI noted to be in old age patient with multiple comorbidities exposed to iatrogenic factors , diagnostic procedure or post surgical in low income countries ,patient tend to be younger and mostly exposed to sepsis , volume depletion and toxins ***(10)***

Risk factors ;

Multiple risk factors documented as environmental ,socioeconomic and cultural and also depend on patient condition . environmental factor as inadequate drinking , waste water ,exposure to infectious disease with inadequate health care some factors related to patient as volume depletion, hypotension, anaemia, hypoxia and use of nephrotoxic drugs, chronic kidney, heart, liver or gastrointestinal disease, diabetes and severe infections and sepsis. Rarer causes include genetic predispositions to myoglobinuria, haemoglobinuria and urolithiasis in ICU ;exposure to nephrotoxic drugs ,chemotherapy for cancer and exposure to opportunistic infection ***(11) .***

Diagnosis;

The best indicator of kidney function is GFR ,GFR is estimated by measuring serum level of endogenous filtration markers as creatinine and small elevation of creatinine usually associated with worse outcomes of AKI , urine output is an important marker of kidney function also. The 2012 KDIGO guideline put the diagnostic criteria for AKI and AKD**,** the KDIGO criteria don't require adequate fluid resuscitation or exclusion urine output obstruction . CKD is an independent risk factor for developing AKI ***(12).***

Although diagnosis of AKI in patient with CKD is very difficult as there is elevation in serum creatinine in patient with CKD and we need to be aware of the baseline but we can define AKI stage 3 as elevation serum creatinine > 4 mg / dl **.** KIDGO use decline in urine output with change in serum creatinine as a markers of AKI occurrence despite decrease urine output is normal as it depend on fluid intake and fluid loss as sweating so it doesn't mean usually tubular injury . the tubular injury not respond to diuretics due to loss of sodium transporter so using single bolus of loop diuretic not followed by increase in urine output (frusemide stress test)indicate tubular injury .***(10).***

Screening and risk assessment ;

Patient with stage 1 AKI ; around half of those patient have histological change on tissue biopsy and elevated biomarkers while in most patient with AKI stage 3 have both . functional biomarkers as serum creatinine and urine output have several limitation as we mentioned before serum creatinine affected by fluid intake and loss and use of diuretics also serum creatinine is not sensitive as it require damage of at least half of nephrons to rise in level . ***(1)***.

AKI biomarkers is divided into functional and damage biomarkers as IL-18 or kidney injury molecule 1 (KIM-1), are available but some limitations exist as poor predictive performance when we don't know the time of kidney insult . ***(13)***.

On the other side damage biomarkers may be used to identify patient at risk for AKI but they have low sensitivity. Other biomarkers that can be measured at the bed side as Cystatin C level and Several neutrophil-gelatinase-associated lipocalin (NGAL) isoforms are released by the kidney and by immune cells NGAL can be used in patients with normal kidney function and in patients with precedent CKD ***Metalloproteinase*** inhibitor 2 (TIMP2) and insulin-like growth factor- binding protein 7 (IGFBP7) are detectable in urine very early during development of AKI ***(14).***

Other methods of kidney function assessment ;

Kidney function can be achieved by collecting urine and a repeated blood sample to determine creatinine clearance. Creatinine clearance used to diagnose impairment of kidney function earlier than estimation of plasma creatinine rise **(15).**

Management ;

It has been found that more than 50 % of patient were managed poorly and about 40% weren't recognized at all. the first step in managing AKI is to determine its cause and recognizing prerenal causes (hypovolaemia) or postrenal causes (outflow obstruction), then identify the cause and treat it ,also general management should be applied . 1/ volume status ; sever and preserved volume depletion can cause. permanent damage to the kidney ***(16).***

Focus on the volume status is an important step in management of AKI**,** volume depletion and dehydration can occurs at patient in hospital as well as patient from the community because of diuretics use or fluid loss from the drain and wound ,intravenous fluid resuscitation should be under direct supervision of a physician and haemodynamic monitoring ***(5).***

Oliguria developed from AKI and fluid overload can occur from the resuscitation, fluid overload can cause venous congestion and affect tissue perfusion which cause direct kidney injury **.** ***(5).*** /haemodynamic management ; general haemodynamic management is applied but also specific management applied according to the type of circulatory shock**.** Mean arterial pressure required to maintain adequate kidney perfusion is 65 mmHg, so hypertensive patient will benefit from higher MAP when in shock Noradrenaline is the first-line choice as a vasopressor for vasodilatory shock. Angiotensin IIin patient with angiotensin II deficiency**,** corticosteroid also used in patient with sever septic shock . 3/nephrotoxic drugs and agents ;

nephrotoxic drugs should be stopped and agents cannot be stopped will be used at required dose under careful monitoring**.** Also radiocontrast agents shouldn't be used till its benefit overcome the risk and used at the lowest volume, fluids containing non-physiologic ratios of sodium and chloride may worsen AKI***(17).***

Balanced electrolyte solutions as lactated Ringer's solution is the preferred one. 4/stage based management of AKI; The 2012 KDIGO AKI guideline emphasizes the importance of AKI staging as a guide to management the prognosis is correlated with the stage and the duration of AKI ***(1)***. for the patient with previous normal kidney function and stage 1 AKI management mainly involves rapid identification of the cause of AKI , in AKI stage2 its necessary to adjust the dose of drug depending on GFR . in stage 1 and 2 retained solutes is not important unless there is underlying CKD although its important to pay attention to fluid regulation as sodium excretion and fluid balance is affected .***(5).***

At stage 3 ,uremic toxins will be accumulated causing electrolytes and acid – base balance disturbance in form of metabolic acidosis and this acidosis will cause cell rupture and k release which cause hyper kalemia also accumulation of uraemia can cause platletes dysfunction and bleeding tendency ***(1)***.

Using loop diuretics will help in fluid and electrolytes as k and Na excretion. Blood glucose control is important because the filtered glucose increases tubular reabsorption load and oxidative stress, which cause kidney tubular injury ***(18).***

However, intensive insulin therapy often has adverse effects and its recommended to maintaining blood glucose concentration at 110–149 mg/dl ***(1)***.

Finally, when in stage 3 AKI KRT becomes necessary. Most of patient with AKI who receive medical tt will show improvement of kidney function within 24 – 48 h and about 30 % of patient will persist for more than 72 h and this carry a worse prognosis and we should reevaluate the general management principals at this point. 4/ kidney replacement therapy ; peritoneal dialysis ,extra corporeal technique is the preferred one and patient who are critically ill and unstable can continue on kidney replacement therapy and once discharge from ICU intermittent techniques, such as sustained low efficiency dialysis or daily intermittent haemodialysis, can be safely used. Continuous veno-venous hemofiltration, continuous veno-venous haemodialysis or continuous veno-venous haemodiafiltration are used The best time to start KRT in patients who are critically ill remains controversial (***19)***.

Acute kidney injury and chronic liver disease

Acute kidney injury is a common complication associated with liver disease especially decompensated liver disease , and the most common types of AKI occur with liver cirrhosis is the pre renal type and acute tubular necrosis . the pre renal type is more benign and respond to good fluid replacement but the renal type have a bad prognosis and require more specific treatment. Once AKI starts it increase morbidity and mortality rate so its important not only to early recognise the case but it require also a rapid management. Renal dysfunction in patient with chronic liver disease has been called hepato renal syndrome which result from wide spectrum of complication mainly portal hypertension that affect systemic hemodynamic then bile acid nephropathy, coagulopathy-induced bleeding from ischemic Acute tubular necrosis , related glomerular diseases (e.g., immunoglobulin, a nephropathy, hepatitis B and hepatitis C-related glomerulonephritis, cryoglobulinemia, membranoproliferative glomerulonephritis), and other comorbid diseases such as inherited cystic diseases . ***(20).***

Diagnostic criteria of AKI in patient with cirrhosis ;

It was used to classify AKI into HRS type 1 and HRS type 2

HRS type 1 ;

Characterized by rapid progressive deterioration of kidney function and elevated serum creatinine above 2.5 mg /dl for more than two weeks . Lack of response to diuretic withdrawal and 2 days volume challenge with albumin 20-25 % in a dose of 1 g /kg/d Cirrhosis with ascites Absence of shock No current or recent use of

nephrotoxic drugs No signs of structural kidney injury (absence of proteinuria >500 mg/d - absence of haematuria >50 RBC_s /HPF –normal finding on renal ultra sound .

HRS type 2 ;

characterized by slow progressive deterioration of kidney function in cirrhotic patient with refractory ascites and elevated serum creatinine (1.5 to 2.5)mg /dl. As serum creatinine is not sensitive biomarker for AKI , the international club of ascites put a diagnostic criteria in 2015 the serum create above 2.5 chriterion and the two weeks threshold for diagnosis of HRS and its subtypes has been removed and the diagnostic criteria now is detecting a change in absolute SCr level of ≥ 0.3 mg/dL or by an increase in SCr ≥ 50% from baseline within 48 h with a lack of volume expansion response without evidence of shock, recent exposure to nephrotoxic agents or preexisting structural renal disease" . In 2011 , AKI defining criteria ***(11)*** were integrated into ICA and Acute Dialysis Quality Initiative ***(21).***

Acute kidney injury (AKI)	Rise in serum creatinine (SCr) of ≥ 50% from baseline or a rise in SCr by ≥ 0.3 mg/dL (26.5 μmol/L) in < 48 h. Hepatorenal syndrome (HRS) type 1 is a specific form of AKI
	Stage 1: Increase in serum creatinine (SCr) ≥ 0.3 mg/dL (26.5 μmol/L) or an increase in SCr 1.5-fold to 2-fold from baseline
	Stage 2: Increase in SCr > 2-fold to 3-fold from baseline
	Stage 3: Increase in SCr > 3-fold from baseline or an increase in SCr ≥ 4.0 mg/dL (353.6 μmol/L) with an acute increase ≥ 0.3 mg/dL (26.5 μmol/L) or initiation of renal replacement therapy
Chronic kidney disease	Glomerular filtration rate (GFR) of < 60 mL/min for > 3 mo, calculated using the MDRD6 formula. HRS type 2 is a specific form of CKD
Acute on chronic kidney disease	Rise in SCr of ≥ 50% from baseline or a rise of SCr by ≥ 0.3 mg/dL (26.5 μmol/L) in < 48 h in a patient with cirrhosis whose GFR is < 60 mL/min for > 3 mo, calculated using the MDRD6 formula

The current hepato renal syndrome diagnostic criteria ; HRS AKI Increase in serum creatinine > 0.3 mg/dL within 48 h OR Increase in serum creatinine >1.5 times (>50% increase) from baseline within 7 d (use creatinine value within the previous 3 months that is closest to presentation as baseline value) . Lack of response to diuretic withdrawal and 2-d volume challenge with albumin 20%–25% in a dose of 1 g/kg/d Cirrhosis with ascites Absence of shock No current or recent use of nephrotoxic drugs (NSAIDs, contrast dye, etc.) No signs of structural kidney injury as Absence of proteinuria (>500 mg/d) , Absence of haematuria

(>50 RBCs per high-power field) and Normal findings on renal ultrasound HRS- NAKI HRS-AKD ; Estimated glomerular filtration rate 50% increase) from baseline within 3 months (use creatinine value within the previous 3 months that is closest to presentation as baseline value) HRS-CKD ; Estimated glomerular filtration rate <60 ml/min/1.73m^2 for >3 months in absence of other potential causes of kidney disease . ***(22).***

Pathophysiology of AKI ;

Kidney injury occurs in chronic liver disease by multiple mechanisms not only hepato renal syndrome Hepato renal syndrome AKI pathophysiology ; Splanchnic vasodilatation ; several mediators, including nitric oxides, prostacyclin, carbon monoxide, epoxyeicosatrienoic acids, glucagon, endogenous cannabinoids, and adrenomedullin result in splanchnic vasodilatation and increasing portal hypertension. Splanchnic vasodilatation lead to a decrease in the effective circulatory volume, reduced renal blood flow and AKI which simulates the renin-angiotensin-aldosterone system (RAAS) and vasopressin, which cause more severe renal vasoconstriction and worsening renal hypoperfusion so the treatment aim at volume expansion as by albumin and splanchnic vasoconstriction . 2/ role of inflammation ; Advanced liver disease with spontaneous bacterial peritonitis (SBP) and renal insufficiency is characterized by high tumour necrosis factor (TNF)-α and interleukin (IL)-6 compared with advanced liver disease with normal renal function ***(23).***

3/adrenal insufficiency ; adrenal insufficiency cause cardiomyopathy in patients with cirrhosis through downregulation of β-adrenergic receptors and the alteration of catecholamines' effects on the systemic vascular tone. Furthermore, the presence of adrenal insufficiency in patients with stable decompensated cirrhosis is associated with circulatory dysfunction, previous history of SBP, and worse survival rate. 4/ cardiac dysfunction ; Cirrhotic cardiomyopathy characterized by decreasing cardiac contractile function with electrophysiological abnormalities without preexisting cardiac disease***(23).***

It result from persistant portal hypertension, which increases the risk of bacterial translocation and portosystemic shunt. Bacterial translocation stimulates the production of systemic inflammatory cytokines and causes endothelial dysfunction**,** also portal hypertension and splanchnic dilation activate the sympathetic nervous system and several neurohormones, including arginine vasopressin AVP, renin, and angiotensin, which affect heart function by increasing afterload and left ventricular end-diastolic pressure. Decreased cardiac output cause renal tissue hypoxia and venous congestion lead to kidney injury and lower glomerular filtration rate ***(24)*** .

Other Pathophysiology involved in AKI in chronic liver diseases ; 1/ role of inflammation , apoptosis and cell death ;

In chronic liver disease, several risk factors as systemic infection, gastrointestinal bleeding, alcohol, viral infection cause hepatic inflammation that result in : Hepatocyte damage that release several damage-associated molecular patterns (DAMPs) from liver cells. (2) Gut immunity impairment that cause translocation of pathogen-associated molecular pattern (PAMPs) from gut organisms . DAMPs and PAMPs stimulate more severe liver damage (ALF, ACLF, and liver cirrhosis) ***(25)*** .

DAMPs as IL-1, IL-33 and bile acid**,** are recognized by several receptors on Kupffer cells resulting in more hepatic damages . the local inflammatory response contributes to the systemic inflammatory response syndrome (SIRS) and turns into the compensatory anti-inflammatory response syndrome (CARS). The CARS is a counter regulatory mechanism against the hyper-inflammatory process. Overwhelming of activated monocyte function may contribute to AKI. Macrophage polarization is related to pro- versus anti-inflammation, then SIRS and CARS in ACLF might be associated with M1 and M2 macrophage polarization, and respectively of Kupffer cells in liver. Oxidative stress and inflammatory cytokines are higher in patients with ACLF than non-ACLF conditions. the severity of ACLF is associated with apoptosis ***(26)***.

Indeed, persistent the inflammatory process is an important risk factor in cirrhotic patients . Therefore, AKI superimposed in ACLF is associated with a 20% increase in mortality depending on AKI severity (more severe with SCr > 1.5 mg/dL). 2/ Role of bile acid: elevated serum bilirubin in chronic liver disease induces bile cast nephropathy and In the more benign form , bile acid accumulation induces proximal tubulopathy

that cause (low uric acid, low phosphate but high bile acid in serum**.** 3/ worsening portal hypertension ; increased intrahepatic resistance is common in progressive ACLF patients and usually results in increased portal hypertension ***(11)*** . This can cause progressive AKI ***(26)***.

4/ Worsening cardiac output: arterial vasodilation in the splanchnic area and peripheral circulation can be noticed in all stages of liver injury, from the early compensated stage to progressive liver decompensation to the late stage of HRS and this can worsen cardiac function The low cardiac output is counteracted by: (1) Several vasoconstriction mediators (including the RAAS, vasopressin, and the sympathetic nervous system); and (2) salt and water retention the low cardiac output and reduced systolic function indicate failure cardiac function which in turn cause more liver damage due to decrease circulatory volume ***(27).***

Management ;

Prevention avoidance of alcohol use. monitoring of serum creatinine and electrolytes when patients are on diuretics. albumin infusion with therapeutic paracentesis. administering antibiotics with episodes of gastrointestinal bleeding. antibiotic prophylaxis against spontaneous bacterial peritonitis. avoiding use of nonselective beta-blockers and nephrotoxic medications such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and nonsteroidal anti-inflammatory drugs. ***(28).***

Long term albumin administration prove to reduce the risk of developing hepato renal syndrome and improve survival rate in one study but patient can get benefit from keeping albumin above 4 g /dl and we should keep in mind that albumin infusion may be associated with volume over load and pulmonary edema. Initial evaluation History taking about use of nephrotoxic drugs, nonselective beta-blocker, radiographic contrast agents, diuretics, lactulose, excess alcohol use, infection and symptoms of vomiting, diarrhoea, hematemesis and melena . Examination to search for infection, assessment volume status and monitoring for hepatic and extrahepatic organ failure**.** Detection the cause of AKI either due to pre renal cause (pre renal azotaemia) , tubular necrosis or hepatorenal syndrome . To exclude structural disease urine analysis should be done for haematuria , proteinuria or abnormal sediments . In hypovolemic AKI ; correction hypovolemia and volume replacement will reduce serum creatinine 0.3 mg/dl of the baseline , then withdrawal diuretics and adjustment dose of lactulose should be done .fluid replacement using albumin 1gm/kg and blood transfusion in case of blood loss to keep haemoglobin above 8 gm /dl ***(21).***

In patient with HRS ; it doesn't respond to fluid challenge only but require careful examination to search for infection as urine and blood culture , chest radiography and diagnostic paracentesis to exclude spontaneous bacterial peritonitis Daily serum creatinine should be assessed to detect AKI stage Pelvi abdominal ultrasonographic ; to detect any structural kidney disease or postrenal obstruction Empirical antibiotic should be started when infection is strongly suspected . ***(28).***

Urinary sodium and urea excretion; in HRS renal sodium excretion usually less than 10 mEq/l but may be high if patient receive diuretics but fractional excretion of sodium FENa (is the percentage of the sodium filtered by the kidney which is excreted in the urine) more accurate than urinary sodium but affected by water reabsorption and used in patient with low urine output .it is calculated in two parts—figuring out how much sodium is excreted in the urine, and then finding its ratio to the total amount of sodium that passed through (aka "filtered by") the kidney. First, the actual amount of sodium excreted is calculated by multiplying the urine sodium concentration by the urinary flow rate. This is the numerator in the equation. The denominator is the total amount of sodium filtered by the kidneys. This is calculated by multiplying the plasma sodium concentration by the glomerular filtration rate calculated using creatinine filtration. This formula is represented mathematically as: $\mathbf{[(Sodium_{urinary} \times Flow\ rate_{urinary}) \div ((Sodium_{plasma}) \times ((Creatinine_{urinary} \times Flow\ rate_{urinary}) \div (Creatinine_{plasma})))] \times 100}$ ***(Espinel, C H. ,1976)*** Low FENa indicate volume depletion but high one indicate sodium loss as in tubular necrosis in cirrhosis, an FENa of < 1% have a senetivity 100% but 14 % specificity in diagnosis of pre renal causes of AKI ***(29).***

Fractional excretion of urea(FEUrea);(based on four simple available tests of the renal function and delivers an indicative percentage of renal failure and its cause using this formula $\mathbf{FEUrea\ (percent) = (S_{Cr} \times U_{Urea}) / (S_{Urea} \times U_{Cr}) \times 100}$) differentiate HRS from pre renal azotaemia or ATN in a better way as Urea, mainly

reabsorbed in the proximal renal tubule and collecting ducts, is not modified by diuretic use and has a higher sensitivity and specificity in differentiation between HRS from non –HRS ***.(30).***

Other biomarkers ; Cystatin C; a low molecular-weight protein produced by all nucleated cells, is usually removed by glomerular filtration so its used to estimate GFR and it usually less affected by age and D.M as serum creatinine , N-acetyl-b-D-glycosaminidase ; is a lysosomal enzyme that is expressed in various tissues, including kidney, liver and lungs. NAG can cleave N-acetyl-glucosamine, a monosaccharide derivative of glucose. Its concentration in urine is minimal due to its inability to cross the glomerular basal membrane. Increased concentration of NAG in urine indicates renal tubular cell breakdown then NAG has become one of the most studied and used biomarkers for the detection and diagnosis of AKI. a-glutathione S-transferase ; The GST protein family divided into 3 major subclasses alpha ,bi, gamma are enzymes which have a role in the detoxification of free radicals .The GST proteins family have been purified from a wide variety of human tissues (e.g. kidneys , testes ovaries , small intestine, liver and adrenal glands). In renal tubules contain alpha and pi forms in high amounts thus GST is a good marker for diagnosis of AKI ***.(30).***

KIM-1 (kidney injury molecule 1) ; A soluble form of human KIM-1 can be detected in the urine of patients with ATN so can be a useful biomarker for renal proximal tubule injury and early diagnosis of the disease **.** neutrophil gelatinase–associated lipocalin (NGAL) (biomarkers of renal tubular injury) ; a protein belonging to the lipocalin superfamily found in activated neutrophil but also it is found that many other types of cells, including in the kidney tubule, may produce NGAL in response to various injuries. urinary NGAL performs better than serum NGAL when measured 2 days following a fluid challenge. The level of NGAL in patients with HRS-AKI is always much lower than that in patients with ATN, even if the HRS-AKI has not responded to treatment**.** also Markers of inflammation such as ∗ interleukin-18 and ∗plasma proteins that have reduced tubular reabsorption because of renal tubular cell damage have also been used (a1-microglobulin, b2-microglobulin, retinol binding protein) ***(31).***

Urinary albumin / creatinine ratio ;

Decompensated cirrhosis (DC) is considered a systemic disease affecting the function of several extra-hepatic organs , so patients with DC have decreased effective arterial blood volume leading to renal hypoperfusion, deterioration of GFR and activation of RAAS system . and as assessment of renal function by serum creatinine is difficult in patients with cirrhosis, due to an enlarged volume of fluid distribution, low protein intake, and decreased creatinine production secondary to muscle atrophy. And the previous biomarkers not widely available so recently studies focus on using urine albumin creatinine ratio (UACR), (UACR) ≥30 mg/g is associated with more severe liver disease and a lower glomerular filtration rate (GFR) and worse LT-free survival in patients with decompensated cirrhosis and that need more studies to be confirmed ***(32)*** **.**

How to calculate ; The amount of a protein called "albumin" is measured in your urine, and that amount is divided by the creatinine also found in your urine. Albuminuria (albumin in the urine) means that there is more albumin in the urine than there should be, which is a sign of kidney damage. Urine albumin creatinine ratio reference ; urine albumin/creatinine ratio (UACR) <30 mg/g is considered to be normal . importance ; In the critical ill patient , elevated albuminuria can reflect illness severity and predict mortality then assessment of albumin/creatinine ratio (ACR) at the bedside has potential clinical benefit and offer rapid results **.** In resource-limited settings access to central laboratory services is limited. Albumin creatinine ratio testing offers the potential to detect markers of kidney damage (albuminuria) and marker of other disease processes **.** urine albumin: creatinine ratio (ACR) has advantages over the dipstick test in sensitivity and quantification of levels. ***(33).***

Pharmacological Treatment ;

1) albumin ; usually the most preferred volume expander as it has anti inflammatory and anti oxidant effect , and administered in a dose of 20–40 g/d together with vasoconstrictors**.** also, other volume expander as crystalloids can be administered. However, albumin is more effective than crystalloids for treatment of HRS-AKI. careful monitoring during albumin administration as it can lead to volume over load and respiratory failure ***(21).***

Vasoconstrictors ; should be used early to reverse the splanchnic vasodilation effect which is the mechanism responsible for HRS , decrease serum creatinine upon using vasoconstrictor by 1 mg /dl reduce mortality rate by 27 % ***(31).***

Vasoconstrictors that used are terlipressin and vasopressin analogue norepinephrine and midodrine, both α-1 adrenergic receptor agonists acting directly on the vascular smooth muscle cells; and octreotide, a somatostatin analogue that acts as an inhibitor of glucagon, a splanchnic vasodilator. Octreotide also has direct splanchnic vasoconstrictive effect, Patients on terlipressin should be monitored for the ischemic complications such as arrhythmia, angina, and splanchnic and digital ischemia. Terlipressin should not be given to patients who experience cardiac or ischemic symptoms, even if the symptoms have subsided following discontinuation of treatment ***(33).***

Terlipressin is given as intravenous bolus doses at 1–2 mg every 6 hours for up to 14 days but is discontinued if there is no response on day 3 or 4. Continuous infusion of terlipressin has similar efficacy with lower total daily dose and fewer side effects . baseline bilirubin less than 10 mg /dl and serum creatinine less than 5 mg/dl ,lower stage of acute on top of chronic liver failure and sustained increase in mean arterial pressure by 5-10 mm Hg predict good response to terlipressin . **(34).**

3) norepinephrine ; 0.5 mg/h and the dose increased every 4 hours by 0.5 mg/h to a maximum of 3 mg/h in order to increase the mean arterial pressure above 10 mm Hg or the urine output to >50 mL/h for at least 4 hours , side effect can occurs as ischemic complications, cardiac arrhythmias, and respiratory complication **(34).**

4) midodrine and octreotide ; that combination works very slowly, but reversal of HRS is possible. Octreotide alone is ineffective, as its splanchnic vasoconstrictive effect is largely counteracted by the large number of vasodilators in the splanchnic circulation. The combination of midodrine and octreotide less effective than terlipressin in improving renal function or HRS reversal, some side effects can be observed as Headaches, blurred vision, cardiac palpitations, and rash with midodrine. Fatigue, nausea, emesis, abdominal pain, or back with octreotide***.(33).***

5)dialysis ; renal replacement therapy (RRT) indicted in HRS as a bridge to liver transplant to treat volume overload, electrolyte derangements, or uraemia**.** Two-thirds of patients with HRS-AKI undergoing RRT pretransplantation recover renal function when they undergo liver transplant. RRT is indicated in patients with all aetiologies of AKI if they are candidates for Liver transplant or if they may become candidates for liver transplant .And In patients who are not candidates for Liver transplant , RRT is indicated if they have ATN, and for a limited period, when the aetiology of AKI is uncertain ***(31).***

6)trans jugular intrahepatic portosystemic shunt ;its not specific for treatment HRS .

7)liver transplantation ; as liver failure is the cause of HRS , so liver transplantation is the main treatment but its too limited due to organ donors problem and many contraindication for transplantation . the patient with HRS AKI has worse pre liver transplantation prognosis than other causes of AKI. ***(28).***

Renal insufficiency post liver transplant and need for renal replacement therapy decrease post transplantation survival**,** Although renal function recovers after Liver transplant, we can not generalize that on all patient , 25% of patients remain dialysis dependent after Liver transplant , especially if they are younger, have chronic renal disease, and require renal replacement therapy before transplantation. however, other studies did not confirm that pretransplantation renal replacement therapy predicted post-transplantation renal insufficiency and mortality**. *(35).* 8)**future directions;

1. Prevention of and protection against kidney injury: better definition of role of intravenous albumin and oral vasoconstrictors
2. Biomarkers for i. Early diagnosis of AKI independent of serum creatinine ii. Distinguishing between types of AKI without kidney biopsy iii. Predicting reversibility and irreversibility
3. Initiation and stopping rules for renal replacement therapy

4. Transplantation i. Maintaining priority for liver transplantation in patients who respond to pharmacological treatment of HRS-AKI ii. Markers to identify patients who require simultaneous liver kidney transplantation vs liver transplantation alone
5. Development and validation of patient-reported outcomes

(22). the recommended dose 1-1.5 mg /kg in the day 1 and 3 with antibiotics help decrease the mortality rate of SBP and AKI***(35).***

Prophylaxis with oral quinolones (norfloxacin 400 mg twice a day for 7 d) is recommended in the high-risk group (low protein in ascites fluid and previous history of SBP) to guard against SBP, intravenous ceftriaxone (1 g/d for 7 d) in patients with active gastrointestinal bleeding. Diuretic-induced AKI is common and result in intravascular volume depletion , electrolyte disturbance as hyperkalaemia from aldosterone antagonists or other potassium-sparing diuretics, require urgent renal replacement therapy, especially in those with renal impairment. Hypokalaemia is a frequent diuretic complication. so, diuretic administration should be avoided in those vulnerable to intravascular volume depletion. nephrotoxic agents, such as radiological contrasts should be used wisely***(36)*** .

Cirrhosis patients with AKI should undergo a full septic workup and be treated with empirical antibiotics as sepsis is an important precipitating factor for organ failure and AKI .

2/ Managements of HRS; If renal function does not improve after adequate volume expansion, HRS-AKI and non-HRS-AKI should be further assessed . In HRS–AKI we should optimize the cardiac output and mean arterial blood pressure (MAP). But it has been found in AKI precipitated with sepsis there was no significant difference in outcomes between targeting the higher MAPs (80-85 mmHg) and the lower MAPs (65-75 mmHg) ***(37)***.

To increase the MAP and cardiac output, intravenous albumin administration and systemic vasoconstrictors are used . systemic vasoconstrictors as vasopressin analogue (terlipressin)**.** ***α-*** adreneregic agonist(norepinephrine), and a combination of α-adrenergic agonist (midodrine) and somatostatin analog (octreotide) it has been found that using terlipressin plus albumin in HRS type 1attenuates the short-term mortality; and using Terlipressin plus albumin or noradrenaline plus albumin is superior to triple therapy with midodrine, octreotide and albumin. Because most HRS-AKI develops in an ACLF and is associated with inflammatory mediators, then the treatment not only depends on hemodynamic restoration but controlling systemic inflammation help in the treatment ***(37)***.

3/ Roles of extracorporeal support systems ; non-HRS-AKI and HRS-AKI in advanced ACLF have higher mortality because they respond poorly to terlipressin and albumin. ACLF with ≥ 2 organ failures (ACLF grade 2-3) is associated with a 60%-75% rate of 28-d mortality, plasmapheresis decrease the severity of ACLF by modulating the immune system . renal and liver support in clinical studies have failed to have any survival advantage. for haemodialysis, continuous renal replacement therapy (CRRT) does not improve mortality in comparison with intermittent haemodialysis; however, its well tolerated in patients with unstable conditions as fulminant hepatic failure as it does not raise intracranial pressure. renal support is not recommended in AKI-superimposed chronic liver disease. But extracorporeal albumin dialysis may improve the condition as it remove excess bilirubin, bile acid, inflammatory cytokines, and endotoxins in systemic circulation The extracorporeal liver support is currently divided into 2 kinds of systems. *1* /Cell-based liver support systems (bioartificial liver support systems); still under trial . 2/Non-cell-based liver support systems: There are two major types ,plasma therapy and albumin dialysis. Plasma therapy has 4 subtypes of techniques: (1) Standard plasma exchange that help the elimination of inflammatory cytokines and endotoxins by using 1.2 L of plasma as fluid replacement. However, it has few advantage (2) High-volume plasma exchange ,it uses a large amount of fresh- frozen plasma as replacement fluid. HVP decrease level of blood ammonia and urea so improve HE there is no evidence on using HPV in ACLF . (3) Plasma perfusion and bilirubin adsorption system and double plasma molecular absorption system. plasma passes through adsorbent which has an adsorption effect on specific molecules (such as bilirubin, bile acid, and related similar molecular structures). The double plasma molecular absorption system is more sophisticated than plasma perfusion and bilirubin adsorption, ***(38).***

(4) Fractionated plasma separation and adsorption (FPSA) . Albumin and other plasma proteins cross the membrane and pass across 2 columns in a series-an anion-exchange column and a neutral resin adsorber. ***(39).***

4/ liver transplantation; liver transplantation is the only treatment in an ACLF setting. the 1-year and 5-year survival rates were 91% and 77%, in HRS and non HRS but patient with underlying. 5/roles of the novel monocytes and macrophage modulators; - Targeting liver macrophage: So far, unfortunately, none of proven macrophage-directed therapies has been recommended in ACLF although a number of immunomodulators including N-acetylcysteine, albumin and glucocorticoids are approved for other immune-related liver diseases ***(39).***

Targeting inhibition of Kupffer cell activation: Inhibition of progression of the early phase of SIRS in ACLF could be attenuate the signal induction for Kupffer cell activation which decrease liver injury**.** In addition, the prevention and treatment of bacterial translocation by appropriate antibiotics is the most effective attenuation of initial innate immune activation leading to the subsequently Kupffer cell inhibition. Targeting inhibition of monocyte recruitment into the liver: The recruitment of monocytes into liver is mediated through chemokine system. Targeting promotion of macrophage differentiation: An early promotion of macrophage differentiation from activated macrophages phenotype into a pro-restorative phenotype might improve the resolution of liver injury. Corticosteroids provides some advantages in the early phase of ACLF but could augment infectious complications in the late phase ***(40).***

Roles of the novel granulocyte colony-stimulating factor therapy; treatment by hematopoietic growth factor to induce immune cells to restore immune haemostasis by improving impaired phagocytosis G-CSF improved the 90-d mortality rate in a randomized trial on 46 patients with ACLF ***(40).***

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