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TOPIC HIGHLIGHT

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Acute renal dysfunction in patients with alcoholic hepatitis

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Abstract

Acute renal dysfunction is common in patients with alcoholic hepatitis (AH). Its presence leads to higher mortality in these patients. Despite advances in medical care, the outcome has changed little over the past decades. Studies using Pentoxifylline and molecular adsorbent recirculation system have shown encouraging data in small studies. Further larger well designed studies are needed to assess these modalities of treatment for the treatment of AH.

Key words: Acute renal dysfunction; Alcoholic hepatitis; Renal failure; Hepatorenal syndrome

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INTRODUCTION

Renal dysfunction can present as acute kidney injury (AKI), defined as an abrupt or rapid decline in renal function, or as chronic kidney disease secondary or concomitant to liver dysfunction. In this chapter we will discuss mechanisms, clinical features and management of AKI in patients with alcoholic hepatitis (AH).

AKI is common among hospitalized patients[1,2], affecting 3%-7% of hospital admissions and 25%-30% of intensive care unit admissions. Patients with AH may have underlying cirrhosis in about 70% of cases[3]. Therefore, AKI in patients with AH could occur due to decompensation of underlying cirrhosis or due to mechanisms peculiar to AH.

PATHOPHYSIOLOGY OF AKI IN ALCOHOLIC HEPATITIS

Mechanisms for AKI due to underlying cirrhosis

AH and cirrhosis are associated with systemic arterial vasodilation because of increased endogenous vasodilators, especially nitric oxide and 3', 5' cyclic guanosine monophosphate[4]. Systemic arterial vasodilation causes a decrease in systemic vascular resistance (SVR) leading to high cardiac output and hyperdynamic circulation[5]. Increase in cardiac output may be insufficient to keep up with a drop in SVR leading to hypotension. Further insult in the form of sepsis or decreased cardiac output may overcome renal blood flow autoregulation, rendering patients prone to pre-renal AKI and acute tubular necrosis (ATN).

In patients with cirrhosis there is increased splanchnic pooling of blood due to portal hypertension. Decreased effective circulatory blood volume leads to activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system. Arginine-vasopressin leads to salt and water retention, further worsening edema and ascites. In addition, there is intense vasoconstriction in an attempt to maintain blood pressure and perfusion to vital organs[6,7].

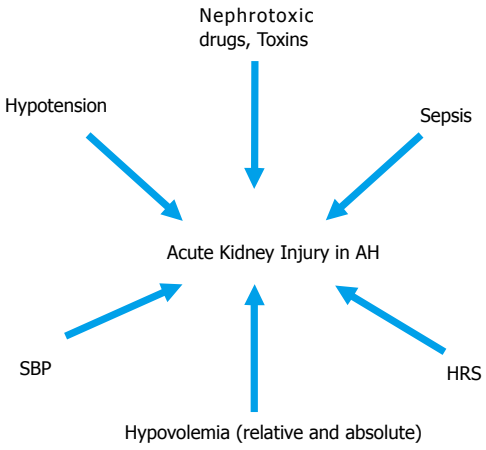

Figure 1 Potential cause of acute kidney injury in alcoholic hepatitis. AH: Alcoholic hepatitis; SBP: Spontaneous bacterial peritonitis; HRS: Hepatorenal syndrome.

Decompensation due to hypovolemia or GI bleeding can make this worse, causing further reduction in glomerular filtration rate (GFR) and predisposing the patient to AKI.

Mechanisms peculiar to alcoholic hepatitis

A number of studies have shown increased gut permeability to endotoxin, bacterial endotoxins and other macromolecules[8,9]. Gut leakiness leading to endotoxemia is a key cofactor for alcoholic steatohepatitis in rats[10]. Bacterial endotoxin (Lipopolysaccharide, LPS) is recognized by Toll-like receptor 4 complex in the liver, which results in increased production of cytokines such as tumor necrosis factor (TNF-α), interleukin (IL)-6, IL-1β and IL-8[11-13]. Studies have shown a linear relationship between TNF-α receptors and mortality from AH[14]. Pentoxifylline is a non-specific phosphodiesterase inhibitor with anti-inflammatory (by TNF-α inhibition) and anti-fibrogenic properties and has been shown to reduce mortality in patients with severe alcoholic hepatitis by significant reduction in the development of hepatorenal syndrome[15]. Elevated TNF-α is significantly associated with chronic kidney disease and proteinuria[16,17].

CAUSES OF ACUTE KIDNEY INJURY IN ALCOHOLIC HEPATITIS

Pre-renal

Patients with AH and cirrhosis may have reduced effective circulatory blood volume and functional hypovolemia. Patients are more susceptible to develop pre-renal azotemia in the presence of true hypovolemia, gastrointestinal bleeding, large volume paracentesis, infections and nonsteroidal anti-inflammatory drugs (NSAIDs)[18-21].

Intrinsic renal

The potential intrinsic causes of AKI in AH are nephrotoxic drugs (e.g. amino glycosides, diuretics and NSAIDs)[22-24], toxins and infections[18]. Rhabdomyolysis[25] and jaundice[26,27] leading to hyperbilirubinemia[28] have also been suggested as causes of intrinsic renal dysfunction. One third of patients with spontaneous bacterial peritonitis (SBP) develop renal dysfunction as a result of reduced effective circulatory volume[29]. Patients with alcohol-induced liver cirrhosis are believed to develop intrinsic renal disease in addition to the above insults[30]. If left untreated, any cause of pre-renal AKI can lead to ATN. (Figure 1)

Hepatorenal syndrome

Hepatorenal syndrome (HRS) is a functional form of renal failure that develops in patients with advanced cirrhosis and ascites. HRS is usually accompanied by severe renal arterial and arteriolar vasoconstriction in the presence of systemic and splanchnic arterial vasodilation leading to low renal perfusion and GFR. HRS can present either as Type-1 (acute developing over few days) or Type-2 (slower in onset over weeks to months)[31]. Patients with AH usually develop type Ⅰ HRS and, without treatment, these patients have a median survival of only 2 wk[32].

DIAGNOSTIC APPROACH TO RENAL DYSFUNCTION IN ALCOHOLIC HEPATITIS

Clinical evaluation

Recent exposure to nephrotoxic drugs, radio contrast agents, surgical or interventional procedures and history of gastrointestinal hemorrhage, vomiting and diarrhea should be excluded. Evaluation should rule out true hypovolemia, infections and sepsis. A complete history and physical can help to exclude vascular and immunological causes of AKI (Table 1, 2). Tense ascites can cause abdominal compartment syndrome defined as intra-abdominal pressure (IAP) of > 20 mmHg and abdominal perfusion pressure < 60 mmHg resulting in decreased renal vein blood flow and renal dysfunction[33]. IAP can be evaluated by intravesical method[34]. Anuria is suggestive of post-renal cause.

Urine evaluation

Microscopic and chemical urinalysis can yield important information for establishing diagnosis. Presence of pigmented granular casts and red blood cell casts (RBC casts) are suggestive of ATN and glomerulonephritis (GN) respectively[35,36]. In contrast, the urine in pre-renal and HRS is generally unremarkable.

Laboratory evaluation

Low urine sodium (< 20 mmol/L) and a high urine osmolality (> 500 mOsm/kg) are suggestive of pre-renal causes or HRS. In contrast, high urine sodium (> 40 mmol/L) and low urine osmolality (< 350 mOsm/kg) suggest intrinsic renal disease or ATN[37,38]. Patients with AKI and advanced liver disease have higher incidence of hyponatremia, SBP, hepatic encephalopathy and higher levels of serum bilirubin, aspartate aminotransferase, alanine aminotransferase, and white cell counts [18].

Table 1 International Club of Ascites criteria for the diagnosis of hepatorenal syndrome

1	Presence of cirrhosis and ascites
2	Serum creatinine > 1.5 mg/dL (or 133 mmol/L)
3	No improvement of serum creatinine (decrease equal to or less than 1.5 mg/dL) after at least 48 h of discontinuing diuretics
4	Withdrawal and volume expansion with albumin (recommended dose: 1 g/kg per day up to a maximum of 100 g of albumin/d)
5	Absence of shock
6	No current or recent treatment with nephrotoxic drugs
7	Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/d, microhematuria (> 50 RBCs/high power field), and/or abnormal renal ultrasound scanning

Table 2 Urinalysis findings in various etiologies of acute kidney injury

AKI type		UA	Urine sodium (mEq/L)	FENA	BUN:Creatinine ratio
Pre-renal		Normal or hyaline casts	< 20	< 1	⩾ 20:1
Intrinsic renal					
	ATN	Muddy brown casts	> 40	⩾ 1	
	GN	Dysmorphic RBC and RBC casts	< 20	< 1	
	AIN	WBC casts and eosinophils	> 20	⩾ 1	
Post-renal		Normal or hematuria	>20	Variable	⩾ 20:1

ATN: Acute tubular necrosis; GN: Glomerulonephritis; AIN: Acute interstitial nephritis; RBC: Red blood cells; WBC: White blood cells; FENA: Fractional excretion of sodium.

MANAGEMENT

Pre-renal and renal

Initial management is similar to the management of AKI of any etiology and includes correction of hypovolemia, electrolyte abnormalities, coagulation disorders and gastrointestinal bleeding. Patients with liver disease are susceptible to develop renal toxicity with diuretics, NSAIDs and amino glycosides[22-24]. The utmost attention should be paid to volume status of patients as they may need fluid challenge to rule out pre-renal hypovolemia as the cause of renal dysfunction. Since the deterioration in patients with advanced liver disease and ascites is associated with SBP and sepsis, one should be vigilant as infection may be the precipitous cause. Renal adjustment of antibiotic dosage may be required secondary to renal dysfunction. If suspected, SBP should be ruled out by performing paracentesis in a patient with ascites. Patients with ascites and other signs and symptoms of fluid overload may require sodium and fluid restriction in addition to frequent paracentesis and albumin administration[39].

Hepatorenal syndrome

HRS is a diagnosis of exclusion. Liver transplantation, often combined with kidney transplantation, is the definitive treatment option. However, as patients with AH are active drinkers, they are not suitable candidates[40].

Vasopressin analogues (terlipressin and orlipressin) have been used in the management of HRS. Their mechanism of action is to induce systemic and splanchnic vasoconstriction leading to increased renal blood flow. Since terlipressin is not available in the United States, other agents such as somatostatin analogues (octreotide) and alpha-adrenergic agonists (midodrine) are used for management of HRS[41,42].

If the patient is non-responsive to vasoconstrictor therapy, a transjugular intrahepatic porto-systemic shunt (TIPS) may result in improvement in renal function in patients with HRS[42]. TIPS is currently recommended only in patients who are eligible for liver transplant.

Patients should be evaluated for Renal Replacement Therapy (RRT) in the event of acute decompensation resulting in metabolic acidosis, electrolyte imbalance and volume overload. RRT has a high incidence of side effects in these sick patients, including arterial hypotension, coagulopathy and gastrointestinal bleeding. Because of the high mortality of HRS, it should be offered as a bridge only to those with the possibility of hepatic recovery or liver transplantation. The three common RRT modalities available are Peritoneal Dialysis, Intermittent Hemodialysis (IHD) and Continuous Renal Replacement Therapy (CRRT). PD is usually contraindicated, secondary to ascites in these patients. CRRT is the preferred modality in these patients since it has an advantage over IHD of better cardiovascular, hemodynamic and Intracranial Pressure stability. The molecular adsorbent recirculation system has shown promising result in patients with AH but needs further evaluation[43-45].

PREVENTION

In patients with spontaneous bacterial peritonitis, administration of albumin in addition to antibiotic therapy (intravenous cefotaxime) significantly lowers the occurrence of HRS and death compared to antibiotics alone[46]. The benefit is believed to be due to plasma volume expansion with intravenous albumin preventing reduction in effective arterial blood volume. As discussed above, in patients with AH, the use of pentoxifylline reduces the incidence of HRS and mortality[15,47].

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