Acute renal dysfunction in patients with alcoholic hepatitis

Robin Arora, Shweta Kathuria, Nishant Jalandhara

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, 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. 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. Systemic arterial vasodilation causes a decrease in systemic vascular resistance (SVR) leading to high cardiac output and hyperdynamic circulation. 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.
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. Gut leakiness leading to endotoxemia is a key cofactor for alcoholic steatohepatitis in rats. 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. Studies have shown a linear relationship between TNF-α receptors and mortality from AH. 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. Elevated TNF-α is significantly associated with chronic kidney disease and proteinuria.

**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). One third of patients with spontaneous bacterial peritonitis (SBP) develop renal dysfunction as a result of reduced effective circulatory volume. Patients with alcohol-induced liver cirrhosis are believed to develop intrinsic renal disease in addition to the above insults. If left untreated, any cause of pre-renal AKI can lead to ATN.

**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). Patients with AH usually develop type 1 HRS and, without treatment, these patients have a median survival of only 2 wk.

**DIAGNOSTIC APPROACH TO RENAL DYSFUNCTION IN ALCOHOLIC HEPATITIS**

**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. 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. IAP can be evaluated by invasivesh method. Anuria is suggestive of post-renal cause.

**Urinary evaluation**

Microscopic and chemical urinalysis can yield important information for establishing diagnosis. Presence of pigmented granular casts and red blood cell casts are suggestive of ATN and glomerulonephritis (GN) respectively. 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. 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.
Absence of parenchymal kidney disease as indicated by proteinuria
No current or recent treatment with nephrotoxic drugs
May 27, 2011
Muddy
BUN:Creatinine
dysmorphic
Presence of cirrhosis and ascites
Serum creatinine > 1.5 mg/dL (or 133 mmol/L)
Urine sodium
Normal or
WBC casts
Withdrawal and volume expansion with albumin (recommended dose: 1 g/kg per day up to a maximum of 100 g of albumin/d)
Absence of shock
No current or recent treatment with nephrotoxic drugs
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 1** International Club of Ascites criteria for the diagnosis of hepatorenal syndrome

| AKI type          | UA   | Urine sodium (mEq/L) | FENA | BUN:Creatinine ratio |
|-------------------|------|----------------------|------|----------------------|
| Pre-renal hyaline casts | Normal or | < 20             | < 1      | ≥ 20:1               |
| Pre-renal intrinsic renal | ATN   | Muddy brown casts   | > 40 | ≥ 1                  |
| Pre-renal intrinsic renal | GN    | Dysmorphic RBC and RBC casts | < 20 | < 1                  |
| Pre-renal intrinsic renal | AIN   | WBC casts and eosinophils | > 20 | ≥ 1                  |
| Post-renal normal or hematuria | 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[40].

**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 alphadrenergic 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[43]. 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[41–43].

**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[40]. 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].

**REFERENCES**

1. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002; 39: 930–936
2. Feest TG, Round A, Hamad S. Incidence of severe acute renal failure in adults: results of a community based study. BMJ 1993; 306: 481–483
3. Bird GL, Williams R. Factors determining cirrhosis in alcoholic liver disease. Med Aspects Med 1988; 10: 97–105
4. Siqueira C, de Moura MC, Pedro AJ, Rocha P. Elevated nitric oxide and 3, 5’ cyclic guanosine monophosphate levels in patients with alcoholic cirrhosis. World J Gastroenterol 2008; 14: 236–242
5. Ellis A, Wendon J. Circulatory, respiratory, cerebral, and re-

---

**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 | < 20             | < 1      | ≥ 20:1               |
| Intrinsic renal   | ATN   | Muddy brown casts   | > 40 | ≥ 1                  |
| Intrinsic renal   | GN    | Dysmorphic RBC and RBC casts | < 20 | < 1                  |
| Intrinsic renal   | AIN   | WBC casts and eosinophils | > 20 | ≥ 1                  |
| Post-renal        | Normal or | ≥ 20:1         |

Hepatic failure in alcoholic hepatitis.
nal derangements in acute liver failure: pathophysiology and management. Semin Liver Dis 1996; 16: 379-388
6 Ginés P, Terra C, Torre A, Guevara M. [Role of albumin in the treatment of hepatic encephalopathy in cirrhosis]. Gastroenterol Hepatol 2005; 28: 80-84
7 Betrosian AP, Agarwal B, Douzinias EE. Acute renal dysfunction in liver diseases. World J Gastroenterol 2007; 13: 5552-5559
8 Bode C, Bode JC. Effect of alcohol consumption on the gut. Best Pract Res Clin Gastroenterol 2003; 17: 575-592
9 Keshavarzian A, Holmes EW, Patel M, Iber F, Fields JZ, Pethkar S. Leaky gut in alcoholic cirrhosis: a possible mechanism for alcoholic-liver induced damage. Am J Gastroenterol 1999; 94: 200-207
10 Keshavarzian A, Farhari A, Forsyth CB, Rangan J, Jakate S, Shaikh M, Banan A, Fields JZ. Evidence that chronic alcohol exposure promotes intestinal oxidative stress, intestinal hyper-permeability and endotoxia prior to development of alcoholic steatohepatitis in rats. J Hepatol 2009; 50: 538-547
11 Takeda K, Akira S. TLR signaling pathways. Semin Immunol 2004; 16: 3-9
12 Latvala J, Hietala J, Koivistio H, Jarvi K, Anttila P, Niemela O. Immune Responses to Ethanol Metabolites and Cytokine Profiles Differentiate Alcoholics with or without Liver Disease. Am J Gastroenterol 2005; 100: 1303-1310
13 Bird GL, Sheron N, Goka AK, Alexander GJ, Williams RS. Increased plasma tumor necrosis factor in severe alcoholic hepatitis. Ann Intern Med 1990; 112: 917-920
14 Spahr L, Giostra E, Frossard JL, Bresson-Hadni S, Rubbia-Brandi L, Hadengue A. Soluble TNF-R1, but not tumor necrosis factor alpha, predicts the 3-month mortality in patients with alcoholic hepatitis. J Hepatol 2004; 41: 229-234
15 De BK, Gangopadhayay S, Dutta D, Baksi SD, Pani A, Ghosh P. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. World J Gastroenterol 2009; 15: 1633-1639
16 Yeo ES, Hwang JY, Park JE, Choi YJ, Huh KB, Kim WY. Tumor necrosis factor (TNF-alpha) and C-reactive protein (CRP) are positively associated with the risk of chronic kidney disease in patients with type 2 diabetes. Yonsei Med J 2010; 51: 519-525
17 Upadhyay A, Larson MG, Guo CY, Vasan RS, Lipinska I, O’Donnell CJ, Katherines S, Meigs JB, Keaney JF, Rong J, Benjamin EJ, Fox CS. Inflammation, kidney function and albuminuria in the Framingham Offspring cohort. Nephrol Dial Transplant 2011; 26: 920-926
18 Wu CC, Yeung TW, Tsai WS, Tseng CF, Chu P, Huang TY, Lin YF, Lu KC. Incidence and factors predictive of acute renal failure in patients with advanced liver cirrhosis. Clin Nephrol 2006; 65: 28-33
19 Moreau R, Lebrec D. Acute renal failure in patients with cirrhosis: perspectives in the age of MELD. Hepatology 2003; 37: 233-243
20 Brater DC, Anderson SA, Brown-Cartwright D. Reversible acute decrease in renal function by NSAIDs in cirrhosis. J Med Sci 1987; 294: 167-174
21 Kim JH, Lee JS, Lee SH, Bae WK, Kim NH, Kim KA, Moon YS. Renal Dysfunction Induced by Bacterial Infection other than Spontaneous Bacterial Peritonitis in Patients with Cirrhosis: Incidence and Risk Factor. Gut Liver 2009; 3: 292-297
22 Cabrera J, Arroyo V, Ballesta AM, Rimola A, Gual J, Elena M, Rodés J. Aminoacylase nephropathy in cirrhosis. Value of urinary beta-2-microglobulin to discriminate functional renal failure from acute tubular damage. Gastroenterology 1982; 82: 97-105
23 Boyer TD, Zia P, Reynolds TB. Effect of indomethacin and prostaglandin A1 on renal function and plasma renin activity in alcoholic liver disease. Gastroenterology 1979; 77: 215-222
24 Sherlock S, Walker JG, Senewiratne B, Scott A. The complications of diuretic therapy in patients with cirrhosis. Ann N Y Acad Sci 1966; 139: 497-505
25 Sood A, Midha V, Sood N. Myoglobinuria: a cause of acute renal failure in alcoholic hepatitis. Am J Gastroenterol 2000; 95: 3669-3670
26 Green J, Better OS. Systemic hypotension and renal failure in obstructive jaundice-mechanistic and therapeutic aspects. J Am Soc Nephrol 1995; 8: 1853-1871
27 Watt K, Uhanova J, Minuk GY. Hepatorenal syndrome: di-agnostic accuracy, clinical features, and outcome in a tertiary care center. Am J Gastroenterol 2002; 97: 2046-2050
28 Rivera-Huizar S, Rincón-Sánchez AR, Covarrubias-Pinedo A, Islas-Carbajal MC, Gabriel-Ortiz G, Pedraza-Chaverri J, Alvarez-Rodriguez A, Meza-Garcia E, Armendariz-Borunda J. Renal dysfunction as a consequence of acute liver damage by bile duct ligation in cirrhotic rats. Exp Toxicol Pathol 2006; 58: 185-195
29 Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorea A, Rimola A, Gassull MA, Arroyo V, Rodés J. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 1994; 20: 1495-1501
30 Newell GC. Cirrhotic glomerulonephritis: incidence, morphology, clinical features, and pathogenesis. Am J Kidney Dis 1987; 9: 183-190
31 Arroyo V, Fernandez J, Ginés P. Pathogenesis and treatment of hepatorenal syndrome. Semin Liver Dis 2008; 28: 81-95
32 Ginés A, Escoress A, Ginés P, Salo J, Jiménez W, Inglada L, Navasa M, Claria J, Rimola A, Arroyo V. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993; 105: 229-236
33 Sugrue M. Abdominal compartment syndrome. Crit Care Clin 2005; 11: 333-338
34 Maerz L, Kaplan LJ. Abdominal compartment syndrome. Crit Care Med 2008; 36: S212-S215
35 Kanbay M, Kasapoğlu B, Perazaella MA. Acute tubular necrosis and pre-renal acute kidney injury: utility of urine microscopy in their evaluation: a systematic review. Int Urol Nephrol 2010; 42: 425-433
36 Hrick DE, Chung-Park M, Sedor JR. Glomerulonephritis. N Engl J Med 1998; 339: 888-890
37 Thadhani R, Pascual M, Bonventre JV. Acute renal failure. N Engl J Med 1996; 334: 1448-1460
38 Brady HR, Singer GC. Acute renal failure. Lancet 1995; 346: 1533-1540
39 van Erpecum KJ. Ascites and spontaneous bacterial peritonitis in patients with liver cirrhosis. Scand J Gastroenterol Suppl 2006; 243: 79-84
40 Chava SP, Singh B, Stangou A, Battula N, Bowles M, O’Grady J, Rela M, Heaton ND. Simultaneous combined liver and kidney transplantation: a single center experience. Clin Transplant ; 24: E62-E68
41 Sandhu BS, Sanyal AJ. Hepatorenal syndrome. Curr Treat Options Gastroenterol 2005; 8: 443-450
42 Wong F, Pantea L, Sniderman K. Midoxurine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2004; 40: 55-64
43 Jalan R, Sen S, Steiner C, Kapoor D, Alisa A, Williams R. Extracorporeal liver support with molecular adsorbents recirculating system in patients with severe acute alcoholic hepatitis. J Hepatol 2003; 38: 24-31
44 Mitzner SR, Stange J, Klammt S, Risler T, Erley CM, Bader BD, Berger ED, Lauchart W, Peszyński P, Freytag J, Hickstein H, Loock J, Löhr JM, Liebe S, Emmrich J, Korten G, Schmidt R. Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl 2006; 12: 277-286
45 Catalina MV, Barrio J, Anaya F, Salcedo M, Rincón D, Clemente G, Bañeres R. Hepatic and systemic haemodynamic changes after MARS in patients with acute on chronic liver failure. Liver Int 2003; 23 Suppl 3: 39-43
46 Sort P, Navasa M, Arroyo V, Aldegue xf, Llanas R, Ruiz-del-
Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Ginès P, Rodés J. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999; 341: 403-409

Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology 2000; 119: 1637-1648

S- Editor Zhang HN  L- Editor Roemmele A  E- Editor Zhang L