Management of cirrhotic ascites in children. Review and recommendations

Part 2: Electrolyte disturbances, nonelectrolyte disturbances, therapeutic options

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ABSTRACT

Ascites is a major complication of cirrhosis. There are several evidence-based articles and guidelines for the management of adults, but few data have been published in relation to children. In the case of a pediatric patient with cirrhotic ascites (PPCA), the following questions are raised: How are the clinical assessment and ancillary tests performed? When is ascites considered refractory? How is it treated? Should fresh plasma and platelets be infused before abdominal paracentesis to prevent bleeding? What are the hospitalization criteria? What are the indicated treatments? What complications can patients develop? When and how should hyponatremia be treated? What are the diagnostic criteria for spontaneous bacterial peritonitis? How is it treated? What is hepatorenal syndrome? How is it treated? When should albumin be infused? When should fluid intake be restricted? The recommendations made here are based on pathophysiology and suggest the preferred approach to diagnostic and therapeutic aspects, and preventive care.

Key words: *albumin, hepatorenal syndrome, hyponatremia, portal hypertension, spontaneous bacterial peritonitis.*

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ELECTROLYTE DISTURBANCES

Hyponatremia *(Table 1)*

Hyponatremia is defined as a serum sodium level ≤ 135 mEq/L;[16,20] however, in cirrhotic patients, lower values are common and in these patients a serum sodium level ≤ 130 mEq/L has been adopted arbitrarily for its definition.[64,65] In general, it is accompanied with an increase of intravascular volume.[8,66] Although it has been described as hypervolemic or dilutional hyponatremia (HH) in the literature regarding the adult population,[6,10,12,13,67] the first term is preferred in pediatrics because excess water relative to sodium also occurs in euvolemic or hypovolemic hyponatremia.[16] As cirrhosis progresses, circulatory dysfunction induces non-osmotic ADH secretion with greater water retention relative to sodium and HH develops.[28,68] The presence of HH should also prompt a search for bacterial infections.[8]

In spite of its slow progression, allowing the CNS to adapt and causing a low incidence of clinical signs, pretransplantation HH is associated with higher morbidity and mortality,[67,69,70] and there is not adequate evidence regarding when it should be treated in asymptomatic patients.[65,67] Although there is consensus not to treat patients when serum values are > 130 mEq/L, values for the discontinuation of diuretics range between ≤ 125 mEq/L and < 120 mEq/L.[6,8-10,13,65,71] Our recommendation is to discontinue diuretics when serum levels are ≤ 125 mEq/L. Although it is controversial, water restriction has become a standard treatment for HH.[71] Correction should be done gradually (≤ 10 mEq/L/day) to prevent pontine myelinolysis syndrome. Given the rapid increases occurred during surgery, blood sodium levels should be maintained at ≥ 130 mEq/L in the immediate pre-transplantation period.[5,9]

TABLE 1. *Recommendations on sodium intake, fluid intake, diuretic and albumin infusion prescription as per the overall assessment of extravascular compartment, blood sodium, blood urea, and diuresis in pediatric patients with cirrhotic ascites*[2,5,6,8,9,66,67]

Serum sodium	Clinical assessment of extracellular compartment	Serum urea	Diuresis	Fluid intake	Sodium intake	Diuretics
≥ 126 mEq/L	Expanded	Normal	1-2 mL/kg/h	Free to cover adequate nutritional intake	Restricted	Yes. Urine sodium should be maintained at ~70 mEq/L. Consider (1)
			> 2 mL/kg/h			
	Contracted	High	≤ 1 mL/kg/h	Intravascular compartment should be increased with H_2O and Na. Infusion of 1 g/kg of albumin 20-25% should be considered if serum albumin is ≤ 2.5 g/dL.		Should be discontinued.

Serum sodium	Clinical assessment of extracellular compartment	Serum urea	Diuresis	Fluid intake	Sodium intake	Diuretics
125 mEq/L-121 mEq/L	Expanded	Normal	1-2 mL/kg/h	Insensible losses (2) + 1/2 diuresis over 24-48 h	Low. Only in case of CNS symptoms, NaCl 3% should be considered.	Should be discontinued.
				Infusion of 1 g/kg of albumin 20-25% should be considered if serum albumin is ≤ 2.5 g/dL.		
			> 2 mL/kg/h	Baseline	Low. Only in case of CNS symptoms, 3% NaCl should be considered.	Urine sodium should be assessed to prescribe diuretics (1)
	Contracted	High	< 1 mL/kg/h	Intravascular compartment should be increased with H_2O and Na. Infusion of 1 g/kg of albumin 20-25% should be considered if serum albumin is ≤ 2.5 g/dL.		Should be discontinued.

Serum sodium	Clinical assessment of extracellular compartment	Serum urea	Diuresis	Fluid intake	Sodium intake	Diuretics
≤ 120 mEq/L	Expanded	Normal	< 1 mL/kg/h	Insensible losses (2) + 1/2 diuresis over 24-48 h	Low. Only in case of CNS symptoms, NaCl 3% should be considered.	Should be discontinued.
				Infusion of 1 g/kg of albumin 20-25% should be considered if serum albumin is ≤ 2.5 g/dL + vasopressor (terlipressin, noradrenaline).		
		High, with major increase in serum creatinine	< 1 mL/kg/h	Insensible losses (2) + 1/2 diuresis over 24-48 h	Low. Only in case of CNS symptoms, NaCl 3% should be considered.	
				Differential diagnoses: ATN or HRS. In case of ATN, it should be treated as such. In case of HRS, infusion of 1 g/kg of albumin 20-25% should be prescribed + vasopressor (terlipressin, noradrenaline).		
	Contracted	High, with normal or mildly increased serum creatinine	< 1 mL/kg/h	Intravascular compartment should be increased with H_2O and Na. Infusion of 1 g/kg of albumin 20-25% should be considered if serum albumin is ≤ 2.5 g/dL.		

PPCA severe malnutrition should be considered when serum creatinine or urea are assessed. The targeted urine sodium for an adequate free water clearance is approximately 70 mEq/L. (1) In case of polyuria with low urine sodium, diuretic doses do not require modifications because free water clearance will correct hyponatremia. On the contrary, if the patient has polyuria and high urine sodium levels, free water clearance will be low and the patient will develop hypovolemic hyponatremia. Renal hypoperfusion in PPCA characterized by oliguria, elevated serum urea, and hyponatremia should prompt infection screening even if the patient has no fever, especially in an euvolemic state. (2) The recommended fluid intake in these cases is the same as insensible losses[15,16] plus 1/2 diuresis. High serum creatinine levels may reflect ATN or HRS. PPCA: pediatric patients with cirrhotic ascites; CNS: central nervous system; ATN: acute tubular necrosis; HRS: hepatorenal syndrome; H2O: water; Na: sodium; NaCl: sodium chloride.

Aquaretic agents have been proposed to treat HH in adults,[8] but they have not been approved for their use in pediatrics.

Symptomatic hyponatremia (neurological signs) requires NaCl 3% correction and diuretic discontinuation.

A minority of patients have hypovolemic hyponatremia,[5,8,66,67] in general, secondary to diuretic use and/or losses from vomiting or diarrhea, with no clinical signs of ascites or edema. Treatment consists of sodium and water replacement and diuretic discontinuation until intravascular volumen is restored.

Hyperkalemia

Aldosterone antagonists are the main cause of hyperkalemia (blood potassium ≥ 5.5 mEq/L) and should be discontinued if the blood potassium level is ≥ 6 mEq/L.

Hypokalemia

Loop diuretics, malnutrition, and steroid use are the main causes of hypokalemia. Furosemide should be discontinued if the blood potassium level is ≤ 3.5 mEq/L.[5] Association of alkalosis and hypokalemia worsens hyperammonemic encephalopathy.

NON-ELECTROLYTE DISTURBANCES

Spontaneous bacterial peritonitis

SBP may cause no symptoms of peritoneal irritation;[72] thus, it should be proactively suspected and sought out (*Table 2*).[5,8] The presence of ≥ 250 neutrophils per mL of ascitic fluid determines its diagnosis, which requires prompt treatment. Lower counts in the presence of a compatible condition should not delay treatment.[72] Ceftriaxone 100 mg/kg/day for 7-10 days may be prescribed for recently hospitalized patients whereas for already hospitalized patients, local epidemiological susceptibility patterns should be considered.[73] Albumin 20-25% at 1 g/kg should be infused to reduce the risk for hepatorenal syndrome (HRS), especially in the presence of increased serum creatinine or urea levels.

Hepatorenal syndrome

HRS is defined as functional renal failure associated with severe liver disease resulting in renal hypoperfusion[74] (*Table 3*). Systemic vasodilation triggers compensatory mechanisms that induce severe renal vasoconstriction. It also involves a reduction in cardiac output.[74,75] In most cases, HRS is characterized by oligoanuria and severe prerenal failure lab tests. Serum creatinine levels, specific for the diagnosis of HRS in adults,[5,6,9] are not sensitive in PPCA (usually malnourished),[70] for whom doubling of previous values has been proposed as an indicator.[76]

HRS is classified into type 1, which progresses rapidly with multiorgan failure and is triggered by an acute event, such as SBP or acute gastrointestinal bleeding, or type 2, which is chronic and develops

TABLE 2. *Recommended criteria for diagnostic paracentesis in pediatric patients with cirrhotic ascites*

Recently hospitalized patients.
Acute increase of ascites.
Malaise. Signs and/or symptoms suggestive of: • peritoneal irritation, • systemic infection, • hepatic encephalopathy, • acute liver and/or kidney impairment with no apparent cause and no acute gastrointestinal bleeding.

TABLE 3. *Diagnostic criteria for hepatorenal syndrome as per the International Ascites Club, updated in 2007*[5,9]

a)	Presence of cirrhotic ascites.
b)	Blood creatinine ≥ 1,5 mg/dL.
c)	Absence of improvement in renal function after 2 days of diuretic discontinuation associated with intravascular compartment expansion with infusion of 1 g/kg of albumin 20-25% (up to 100 g/day).
d)	Absence of renal parenchymal disease (defined by protein in urine > 500 mg/day and/or microscopic hematuria > 50 red blood cells/high resolution field, and normal kidney ultrasound).
e)	Absence of shock.
f)	The patient should not be receiving and/or should not have recently received nephrotoxic drugs, especially non-steroidal anti-inflammatory drugs.

when severe renal vasoconstriction occurs in association with a reduction in cardiac output (secondary to heart dysfunction) causing insufficient renal perfusion. Both HRS types differ in their course and prognosis and should be considered different complications instead of different manifestations of the same disorder.[77] Management of type 1 HRS includes treating the triggering factor and administering albumin 20-25% infusion associated with vasopressors (terlipressin, noradrenaline) to increase EAV and reduce peripheral vasodilation.[5,6,13,74,78,79] Although mortality has decreased over the past years, it is still high.[80] Patients with type 2 HRS should be assessed for liver transplantation.[13]

Cirrhotic patients are frequently exposed to situations predisposing to non-HRS renal failure, such as sepsis, acute gastrointestinal bleeding, diarrhea, hypovolemia caused by diuretics and nephrotoxic drugs (non-steroidal anti-inflammatory drugs such as ibuprofen, aminoglycosides, amphotericin B deoxycholate, vancomycin).[38] In general, in these cases, renal function improves once the triggering situation is resolved.

THERAPEUTIC OPTIONS

Albumin prescription

Although portal hypertension and increased splanchnic blood flow are the main factors for ascites, hypoalbuminemia also contributes to its development. However, whereas albumin infusion associated with furosemide is recommended for some children with idiopathic nephrotic syndrome,[42,81,82] there is not adequate evidence regarding the level of serum albumin required for infusion in PPCA.

In adults with SBP, there is adequate evidence that albumin infusion as adjuvant therapy to antibiotic therapy reduces the risk for renal involvement and mortality.[43,44,83] In the case of PPCA with SBP, we favor a single infusion of 1 g/kg of albumin 20-25%. The optimal dose is yet to be determined.[43]

There is also good-quality evidence that albumin infusion reduces morbidity and mortality in cirrhotic adults when large-volume therapeutic paracentesis is performed.[45,84] A recent observational study in children with these characteristics showed similar results.[59] There is consensus that albumin infusion plays a significant role in HRS management.[5,6,8,9,76] For this reason, it is also recommended in these situations.

It has been reported that weekly albumin infusions reduce the length of stay in the hospital and increase life expectancy in adults with cirrhotic ascites;[85,86] however, given that the cost-effectiveness for this treatment has not been analyzed, it is not recommended as standard treatment for patients with cirrhotic ascites.[5,8,31] Albumin infusion is also recommended for pediatric patients with a blood albumin level ≤ 2.5 g/dL to promote extravascular water reabsorption, associated with loop diuretics to produce more diuresis.[2,87] It has been observed that albumin infusion and water restriction correct HH in children, and other authors have proposed this treatment for adults,[88] but there are no good-quality studies to support this recommendation.[8,89] Albumin infusion alone or together with vasopressors may also be useful for the management of HH.

Taking albumin's cost into account we propose using the entire vial with monitoring for cardiac overload signs,since cirrhotic cardiomyopathy has to be considered. Maximum doses should not exceed 1.5 g/kg or 100 g (dose for the diagnosis of HRS in adults).[6,9,44]

Furosemide prescription

Furosemide should be reserved to the following cases: a) cardiac overload[8,12,75] in HRS or following albumin infusion in large-volume paracentesis in the setting of cirrhotic patients with cardiomyopathy; b) to increase potassium excretion in patients with hyperkalemia induced by antialdosterone agents; and c) to increase sodium excretion once maximum doses of aldosterone antagonists have been reached. It may also be prescribed as adjuvant therapy to albumin infusion for patients with a blood albumin level ≤ 2.5 g/dL. Patients with SBP or following large-volume paracentesis have hemodynamic impairment,[43-45,90,91] so the use of furosemide in these situations is discouraged when albumin is infused as EAV reduction may be exacerbated and kidney function may be impaired.

Water restriction

Water restriction (1000 mL/day) is the usual treatment for adult patients with HH and normal serum creatinine and urea levels; however, its effectiveness has been questioned.[6,8,9,13,71] Our recommendation for PPCA with HH, blood sodium level ≤ 125 mEq/L, and normal serum creatinine and urea levels is to restrict fluid intake to insensible losses[15,16] plus half of the diuresis over a maximum of 24-48 hours to avoid hypovolemic stimulus and low nutrient intake.

Fluid restriction is not necessary in the case of a serum sodium level > 125 mEq/L;[2,9] however, in patients with a serum sodium level between 126 mEq/L and 130 mEq/L, excessive water intake should be prevented, and consideration should be given to the fact that many drugs are administered with glucose solutions or water.

FINAL COMMENT

There is not enough information to make recommendations on the use of the transjugular intrahepatic portosystemic shunt (TIPS), beta blockers, vaptanes or antibiotic prophylaxis in PPCA. ■

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