# RESEARCH LETTER

## Aldosterone Antagonist Dosing and the Risk of Hyponatremia in Patients With Cirrhosis and Ascites

Ascites is a common decompensating event in cirrhosis.[1] For initial treatment, major liver societies recommend spironolactone 100 mg daily with or without furosemide 40 mg daily.[2] Although supporting data are lacking, the generally accepted dosing ratio of spironolactone to furosemide is 5:2 so as to maintain potassium equilibrium.[2] However, aldosterone antagonists are a common cause of hyponatremia because they induce natriuresis at the distal tubule and collecting ducts, leaving scant opportunity for sodium reabsorption. Indeed, several large studies of patients presenting with hyponatremia show a strong association with potassium-sparing, but not loop, diuretics.[3,4] As hyponatremia correlates with increased mortality in patients with cirrhosis,[3–8] we examined the influence of aldosterone dosing on serum sodium concentrations and clinical outcomes in a cohort of patients with cirrhosis who were newly initiated on diuretic therapy for ascites.

This is a retrospective, multicenter study of patients with cirrhosis and ascites who received care in the Mass General Brigham system and were simultaneously initiated on a loop diuretic and aldosterone antagonist for treatment of ascites. Dosing of each diuretic was dichotomized as high dose (spironolactone $\geq$100 mg, furosemide $\geq$40 mg) or low dose. The amount of ascites was quantified on the closest abdominal imaging study before diuretic initiation. The primary outcome was development of moderate hyponatremia (<130 mEq/L) within 1 year of diuretic initiation. Secondary outcomes included profound hyponatremia (<125 mEq/L), extreme hyponatremia (<120 mEq/L), hypokalemia (<3.5 mEq/L), hyperkalemia (>5.2 mEq/L), number of hospital admissions, and death. Multivariable and inverse probability of treatment-weighted Cox regression with propensity score adjustment were performed on both an intention-to-treat (ITT) and censorship at dose change (CDC) basis.

A total of 206 patients met entry criteria. All subjects received furosemide and spironolactone; none were receiving potassium supplements. Baseline characteristics dichotomized by spironolactone dose are shown in Table A1. The cohorts were generally well matched, with similar baseline creatinine and amount of ascites. The high-dose cohort had a slightly lower baseline sodium and higher international normalized ratio and Model for End-stage Liver Disease (MELD)-Na. The 77 patients (37%) who developed at least moderate hyponatremia experienced more hospitalizations (5.0 vs 2.7; $P < .01$) and had increased mortality at 1 year (22% vs 5%; $P < .01$). Patients receiving high-dose spironolactone had a greater likelihood of developing moderate, profound, or extreme hyponatremia (Table). In contrast, there was no difference in moderate hyponatremia in those receiving high- vs low-dose furosemide (40% vs 35%; $P = .56$).

On multivariable analysis controlling for degree of ascites and MELD-Na, patients on high-dose spironolactone manifested an increased hazard of moderate hyponatremia by ITT (HR, 2.4; 95% CI, 1.01–5.5; $P = .05$) and trended toward an increased hazard of moderate hyponatremia by CDC (HR, 2.3; 95% CI, 0.9–5.6; $P = .08$). The high-dose spironolactone cohort also showed a strong trend toward moderate hyponatremia by inverse probability of treatment-weighted Cox regression with propensity score adjustment on ITT (HR, 3.1; 95% CI, 0.9–10.9; $P = .08$) and CDC (HR, 2.1; 95% CI, 0.9–4.5; $P = .07$) analysis and exhibited a significantly shorter time to hyponatremia (Figure A1). In contrast, patients on high-dose furosemide trended toward a reduced hazard of hyponatremia by ITT (HR, 0.6; 95% CI, 0.3–1.3; $P = .19$) and CDC (HR, 0.6; 95% CI, 0.3–1.6; $P = .34$). Within the high-dose spironolactone cohort, 47 (56%) were censored for dose change, 21 of whom had not had an episode of moderate hyponatremia at the time of censorship; only 2 (10%) of these patients subsequently developed hyponatremia within the study period. Patients administered high- vs low-dose spironolactone also trended toward an increased likelihood of hypokalemia (57% vs 45%; $P = .11$) and hyperkalemia (46% vs 34%; $P = .08$). Although the majority of patients (77%) received standard 5:2 spironolactone to furosemide dosing, 20% received lower and 3% higher ratios. As the dose of spironolactone to furosemide increased, there was a trend toward higher rates of moderate hyponatremia with no appreciable effect on the incidence of hypokalemia or hyperkalemia.

Our data suggest that patients with cirrhosis and ascites who are initiated on combination diuretic therapy with a spironolactone dose of 100 mg or greater (regardless of furosemide dosing) have a 3-fold increased hazard of developing moderate hyponatremia. These findings are consistent with prior reports that potassium-sparing (but not loop) diuretics heighten the risk of hyponatremia in various clinical settings.[3,4] Notably, patients with decompensated cirrhosis are particularly susceptible to aldosterone antagonist-induced hyponatremia, as reduced intravascular volume activates the renin-angiotensin-aldosterone system and also increases circulating antidiuretic hormone levels. Under these conditions, antagonism of aldosterone effectively leads to unopposed free water reabsorption. In line with prior

**Table.** Outcomes Stratified by Spironolactone Dose

| | High-dose spironolactone (dose of ≥100 mg) | Low-dose spironolactone (dose of <100 mg) | *P* value |
|---|---|---|---|
| n | 84 | 122 | |
| Sodium <130 mEq/L | 39 (46%) | 38 (31%) | .03 |
| Sodium <125 mEq/L | 19 (23%) | 11 (9%) | .006 |
| Sodium <120 mEq/L | 9 (11%) | 4 (3%) | .03 |
| Potassium <3.5 mEq/L | 48 (57%) | 55 (45%) | .11 |
| Potassium >5.2 mEq/L | 39 (46%) | 41 (34%) | .08 |
| Number of admissions[a] | 2 (1–5.4) | 1.7 (0–5.1) | .44 |
| Death | 11 (13%) | 12 (10%) | .46 |
| Liver transplantation | 0 (0%) | 4 (3%) | .09 |
| Follow-up period, d | 275 (±130) | 293 (±122) | .30 |

[a]Number of admissions per patient during observation period, extrapolated to 365 days.

studies showing that hyponatremia is associated with poorer outcomes in individuals with cirrhosis,[6,7] we observed significantly higher mortality and increased hospitalization rates in patients who manifested a serum sodium below 130 mEq/L. Hence, our findings have potentially serious clinical ramifications.

While co-administration of a potassium-sparing and loop diuretic has been shown to control ascites more rapidly than monotherapy, there are scant data to guide optimal dosing.[2] Long-standing consensus holds that a 5:2 ratio of spironolactone to furosemide is ideal for maintaining potassium equilibrium. However, our data challenge this dogma, as we show strong trends toward an increased incidence of both hyperkalemia and hypokalemia in patients administered higher dose spironolactone despite a 5:2 dosing ratio, whereas a ratio below 5:2 was not associated with a higher likelihood of either hyperkalemia or hypokalemia. Guidelines also recommend salt restriction (2 g or 90 mmol/d) in the management of ascites[2]; however, there are conflicting data regarding the effectiveness of a sodium-restricted diet to control ascites[9] and concern that it may exacerbate malnutrition and worsen outcomes in patients with cirrhosis.[10]

The strengths of our study include the large cohort size and granular chart review to ensure the accuracy of diuretic dosing and timing. The concordance of the ITT and CDC analyses supports that the findings are not skewed by dose adjustments. We attempted to account for confounding by indication through a priori adjustment for the amount of ascites and MELD-Na in the Cox regression, as well as by using propensity score adjustment that included all relevant clinical data that would inform diuretic dose selection. The potential exists that our findings may have been confounded by the modestly higher acuity of liver disease in the high-dose spironolactone cohort, as evidenced by an increased prevalence of hepatic encephalopathy and higher international normalized ratio and MELD-Na. We attempted to control for this possibility by adjusting for MELD-Na in the multivariable analyses. We could not assess the effect of diuretic monotherapy as patients rarely were initiated on a single agent.

In summary, our data support that in patients with cirrhosis and ascites, doses of spironolactone ≥100 mg daily substantially increase the likelihood of hyponatremia without altering the risk of hyperkalemia or hypokalemia despite concurrent furosemide administration. As hyponatremia is associated with poorer clinical outcomes, we submit that initial dosing of spironolactone may be more appropriately limited to 25–50 mg and that further upward dose adjustments primarily be with the concurrent loop diuretic. Ultimately, prospective studies addressing the efficacy and safety of diuretic dosing regimens for the management of ascites in cirrhosis are warranted.

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## Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.06.014.

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***Abbreviations used in this paper:*** **CDC, censorship at dose change; ITT, intention-to-treat; MELD, Model for End-stage Liver Disease**

**Most current article**



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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

**Data Transparency Statement:**
De-identified data, analytic methods, and study materials can be made available to other researchers upon request and will be available only via secure, encrypted data transfer.