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Association of Hyponatremia on Mortality in Cryptococcal Meningitis: A Prospective Cohort

Short Title: Hyponatremia in Cryptococcal Meningitis

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Abstract:

Background: Sodium abnormalities are frequent in CNS infections and may be caused by cerebral salt wasting, syndrome of inappropriate antidiuretic hormone secretion (SIADH), or medication adverse events. In cryptococcal meningitis, the prevalence of baseline hyponatremia and whether hyponatremia adversely impacts survival is unknown.

Methods: We conducted a secondary analysis of data from two randomized trials of HIV-infected adult Ugandans with cryptococcal meningitis. We grouped serum sodium into 3 categories: <125, 125-129, and 130-145 mmol/L. We assessed whether baseline sodium abnormalities were associated with clinical characteristics and survival.

Results: Of 816 participants with cryptococcal meningitis, 741 (91%) had a baseline sodium measurement available: 121 (16%) had Grade 3-4 hyponatremia (<125 mmol/L), 194 (26%) had Grade 2 hyponatremia (125-129 mmol/L), and 426 (57%) had a baseline sodium of 130-145 mmol/L. Hyponatremia (<125 mmol/L) was associated with higher initial CSF quantitative culture burden (P<.001), higher initial CSF opening pressure (P<0.01), lower baseline Glasgow Coma Score (P<0.01), and a higher percentage of baseline seizures (P=.03). Serum sodium <125 mmol/L was associated with increased 2-week mortality in unadjusted and adjusted survival analyses; adjusted hazard ratio of 1.87 (95%CI, 1.26 to 2.79; p<0.01) compared to those with sodium 130-145 mmol/L.

Conclusions: Hyponatremia is common in cryptococcal meningitis and is associated with excess mortality. A standardized management approach to correctly diagnose and correct hyponatremia in cryptococcal meningitis needs to be developed and tested.

Introduction:

Hyponatremia is the most frequent electrolyte abnormality in Central Nervous System (CNS) disease, resulting from failure of neuroendocrine regulatory mechanisms to maintain salt and water balance [1]. Coupled with CNS disease, hyponatremia may exacerbate cerebral edema and increase intracranial pressure due to hypoosmolality [2]. There are two main mechanisms of hyponatremia in CNS disease; the first is cerebral salt wasting caused by excess brain natriuretic peptide leading to renal salt wasting and a volume contracted state, the second is the syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH), a volume expanded state from ADH-mediated water retention [3]. Differentiating cerebral salt wasting from SIADH is complex but important for management as treatment for SIADH with fluid restriction would be detrimental in the volume contracted state of cerebral salt wasting. Ultimately, the ability to determine the volume status (low versus high effective arterial blood volume) is pivotal in differentiating between cerebral salt wasting and SIADH.

Hyponatremia in the context of CNS infections has been well documented in tuberculous meningitis (TBM). Approximately 40-50% of TBM patients present with hyponatremia which is most commonly attributed to cerebral salt wasting [3, 4]. Sodium levels below 125 mmol/L, among adults with TBM, are associated with up to a threefold increase in mortality compared to normal sodium levels [5]. Hyponatremia in CNS cryptococcosis, however, has not been well described. Published literature on the topic of hyponatremia in cryptococcal meningitis (CM) is limited to a few case reports in which cases of both cerebral salt wasting and SIADH are described [6-9]. In the published literature, sodium levels and the general condition of patients with clinical and laboratory findings consistent with cerebral salt wasting improved with administration of isotonic saline and fludrocortisone, whereas those with SIADH improved with treatment of cryptococcal meningitis.

Severe hyponatremia, irrespective of the cause, may cause altered mental status, which in itself is an independent predictor of cryptococcal mortality [10]. However, it is unclear whether hyponatremia is independently associated with adverse clinical outcomes in cryptococcal meningitis. In this prospective study of adults with HIV-associated cryptococcal meningitis in Uganda, we assessed whether baseline sodium abnormalities are associated with excess mortality.

Methods:

We conducted a prospective cohort study of adult Ugandans with HIV-associated cryptococcal meningitis from 2015-2020 as a secondary analysis of two randomized trials, the "Adjunctive sertraline for HIV-associated cryptococcal meningitis" trial (ASTRO-CM) and the AMBIsome Therapy Induction OptimisatioN trial (AMBITION) [11, 12]. All participants with suspected meningitis were screened for enrollment into ASTRO-CM and those found to have a first episode of cryptococcal meningitis were enrolled into the randomized trial. Participants found to have cryptococcal meningitis relapse were consented to receive open-label, compassionate use of sertraline. In the ASTRO-CM trial, participants were randomly assigned (1:1) to receive standard therapy with 7-14 days of intravenous amphotericin B and oral fluconazole with either adjunctive sertraline or placebo. Participants enrolled in the AMBITION trial were randomly assigned (1:1) to receive a single high dose of liposomal amphotericin B (AmBisome, Gilead Sciences Inc) in combination with 14 days of fluconazole and flucytosine or seven days of standard amphotericin B deoxycholate in combination with seven days of flucytosine followed by seven days of high-dose fluconazole. For both trials, participants were enrolled from two referral hospitals in Kampala and Mbarara with follow up for at least 10 weeks. Both trials are described in detail elsewhere [13, 14].

A diagnosis of cryptococcal meningitis was made based on a positive cryptococcal antigen test (CrAg lateral flow assay, IMMY) in both the serum and cerebrospinal fluid (CSF). All participants found to have an elevated CSF protein and clinical features suggestive of tuberculous meningitis had a CSF Xpert MTB/RIF Ultra performed at baseline. Serum sodium was measured for all enrolled participants at baseline, days 7, and 14 from initiation of antifungal therapy. All participants routinely received at least one liter of intravenous normal saline (0.9% NaCl) before and after each infusion of amphotericin which itself was administered in one liter of 5% dextrose.

Patient Consent Statement

The design of both clinical trials was approved by local ethical committees and conformed to Ugandan clinical trial standards. Approval for the ASTRO-CM trial was obtained from the Uganda National Council for Science and Technology, the Mulago institutional review board in Uganda, and the institutional review board at the University of Minnesota. Approval for the AMBITION trial was obtained from the London School of Hygiene and Tropical Medicine Research Ethics Committee and the Mulago institutional review board in Uganda. All participants provided written informed consent at time of cryptococcal diagnosis for study participation.

We assessed whether baseline sodium abnormalities were associated with excess mortality. We categorized serum sodium levels as normal or Grade 1 (130-145 mmol/L), Grade 2 (125-129 mmol/L), and Grade 3-4 (<125 mmol/L) hyponatremia per NIAID Division of AIDS (DAIDS) toxicity table (version 2.1 - July 2017) [15]. Four sodium values >150 mmol/L and four sodium values between 146 and 150 mmol/L were excluded from the comparator group as they were considered to be above the normal serum sodium range. The primary outcome was time from the baseline sodium measurement to death in the first two weeks. We additionally assessed 30-day mortality.

We summarized baseline demographic variables and clinical characteristics by serum sodium group using percentages and medians with interquartile ranges (IQR). We compared medians with the Kruskal Wallis test and proportions with the Chi-squared test. We examined the association between baseline sodium and survival using Cox proportional hazards models and Kaplan-Meier curves. All models were adjusted for the following variables define apriori: Glasgow Coma Scale (GCS) score <15 versus 15, baseline cerebrospinal fluid (CSF) cryptococcal quantitative culture, and study. A two-sided type I error of 0.05 was used. We performed all analyses with SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results:

From March 2015 to May 2017, a total of 524 participants were enrolled in the ASTRO-CM trial and from October 2018 to February 2020, a total of 308 were enrolled in the Uganda sites of the AMBITION trial. No trial participants had microbiologically confirmed cryptococcal and tuberculous meningitis co-infection. Among 816 trial participants, 90% (749/816) had serum sodium measured at baseline, of which 91% (741/816) had a serum sodium ≤145 and included in this analysis. Over half (52.2%, n=426) of participants had normal or Grade 1 baseline sodium 130-145 mmol/L, 23.8% (n=194) had Grade 2 hyponatremia (125-129 mmol/L), and 14.8% (n=121) had Grade 3-4 hyponatremia (<125 mmol/L). Eight participants (0.01%, n=8) had a baseline serum sodium >=145 mmol/L, were classified as hypernatremia, and excluded from this analysis. Median sodium was 134 mmol/L (IQR: 132,137) among those with Grade 1 baseline sodium, 128 mmol/L (IQR: 126, 128) among those with Grade 2, and 122 mmol/L (IQR: 119,123) among those with Grades 3-4. Overall, serum sodium levels improved overtime within all three sodium categories (**Supplemental Tables 1-4**).

Baseline demographics and clinical characteristics are summarized by the severity of hyponatremia in Table 1. Hyponatremia was found to be associated with altered mental status (GCS<15) and self-reported seizures at baseline. Half (52.5%) of the participants with

sodium<125 mmol/L presented with GCS<15 as compared to 45.1% of participants with sodium 125-129 mmol/L and 35.5% with sodium 130-145 mmol/L (p<0.01). Participants with severe hyponatremia were also more likely to present with a history of self-reported seizures at baseline (24.2% sodium<125 mmol/L vs. 13.5% sodium 125-129 mmol/L vs. 15.2% sodium 130-145; p=0.03). Hyponatremia was also associated with increased CSF opening pressures (p<0.01) and a higher CSF fungal burden. CSF cryptococcal quantitative culture was significantly greater in persons with severe hyponatremia at baseline (median 4.8 $\log_{10}$ CFU/mL, [IQR: 4.2, 5.9] for sodium<125 mmol/L, median 4.7 [IQR: 2.8, 5.4] for sodium 125-129 mmol/L, and median 4.3 [IQR: 2.4, 5.5] $\log_{10}$ CFU/mL for sodium 130-145 mmol/L; p<.001).

Severe hyponatremia (sodium <125 mmol/L) was associated with mortality in both unadjusted and adjusted survival analyses. The proportion of deaths occurring by two weeks is higher in severe hyponatremia (<125 mmol/L) at 39.7% compared to 24.2% in moderate hyponatremia (125-129 mmol/L) and 16.9% with sodium 130-145 mmol/L (Chi-square test p<0.001, **Table 2**). When compared to participants with baseline sodium 130-145 mmol/L, a baseline sodium <125 mmol/L was associated with nearly 2-fold higher 2-week (Adjusted Hazard Ratio = 1.87; 95%CI, 1.26 to 2.79; p<.01) and 30-day mortality (Adjusted Hazard Ratio = 1.88; 95%CI, 1.33 to 2.66; p<.001) (**Table 2**). Overall, cumulative probability of 2-week survival was lowest in the severe hyponatremia group (<125 mmol/L) as illustrated in **Figure 1**.

Discussion:

Among Ugandan adults with cryptococcal meningitis enrolled in two clinical trials, we observed that severe baseline hyponatremia (<125 mmol/L) is common and associated with nearly 2-fold higher in-hospital mortality. This risk is consistent when assessing 2-week and 30-day mortality. This is not surprising as severe hyponatremia is a well-established poor prognostic indicator in TB meningitis, bacterial meningitis, and among critically ill patients in general [5, 16, 17]. Our study is the first to confirm that baseline severe hyponatremia is also a

poor prognostic indicator in cryptococcal meningitis and may act as a surrogate marker of severe cryptococcal meningitis.

Our study population was comprised of individuals with cryptococcal meningitis in the context of advanced HIV disease, therefore the etiology of hyponatremia is likely multifactorial including non-CNS complications of advanced HIV disease such as poor intake, gastrointestinal losses, drugs, endocrine disorders, liver, kidney, and heart failure. Although non-CNS causes of hyponatremia is possible, we hypothesize that in cryptococcal meningitis, CNS cryptococcosis directly leads to the development of hyponatremia. While we were unable to differentiate between cerebral salt wasting and SIADH in our studies, we observed that individuals with severe hyponatremia present with more severe CNS disease as characterized by altered mental status, seizures, elevated intracranial pressures, and higher CSF fungal burden. Thus, it is highly likely that baseline hyponatremia, in this cohort, is attributable to CNS cryptococcosis as opposed to non-CNS causes. Further, baseline hyponatremia may be used as a surrogate marker of increased intracranial pressures, especially in settings where manometers are not available to measure opening pressures.

The evaluation of hyponatremia in our studies was limited by the lack of access to testing of urine electrolytes, serum osmolality, and acid-base status, as these are not readily available in settings where the burden of cryptococcal meningitis is highest. Furthermore, cryptococcal meningitis guidelines for resource-limited settings focus on the management of electrolyte imbalances of potassium and magnesium with no mention to the evaluation and management of hyponatremia. A rational approach to evaluating the etiology of hyponatremia in persons presenting with cryptococcal meningitis would be to initially exclude non-CNS causes of hyponatremia followed by differentiation between SIADH and cerebral salt wasting to determine the optimal treatment. We suggest a pragmatic approach to the evaluation and management of severe hyponatremia among patients with cryptococcal meningitis presenting with serum

sodium <125 mmol/L that can be easily implemented in both low and high resource settings (**Figure 2**).

In cryptococcal meningitis, symptoms of severe hyponatremia including altered mental status and seizures are common and occurs with moderate frequency. Treatment of cryptococcal meningitis including management of raised intracranial pressure, seizures, and initiation of amphotericin based antifungal therapy will lead to early improvement of hyponatremia in most cases. Amphotericin therapy requires specific consideration as 1) preexisting hyponatremia predisposes to declines in glomerular filtration rate thereby exasperating electrolyte abnormalities and 2) administration of 500 – 1000 mL of 0.9% sodium chloride (normal saline) prior to and after amphotericin infusion is needed to prevent nephrotoxicity. If hyponatremia persists with initiation of cryptococcal therapy, the assessment of volume status will be crucial in differentiating between either cerebral salt wasting or SIADH and directing the appropriate management.

Mortality among in-patients with HIV-associated cryptococcal meningitis remains high (approximately 20%) even with the most efficacious antifungals currently available in sub-Saharan Africa. Our group has previously shown that increased CSF lactate and low cerebral tissue oxygenation are associated with excess mortality in cryptococcal meningitis [18-20]. Taken together, these findings suggest that optimizing neurological supportive care or critical care among patients with cryptococcal meningitis in resource limited settings, in addition to providing optimal antifungal therapy, could further improve treatment outcomes.

Our study is not without limitations. We did not have enough data to determine the etiology and pathophysiological mechanism of hyponatremia. Our statistical analysis was unable to include baseline opening pressure as a covariate in the adjusted mortality models as we would have had to exclude a significant number of participants from our analysis due to missing data. While we recognize that this is significant limitation, given that the association between baseline severe hyponatremia and mortality is preserved even after adjusting for previously known

predictors of mortality and increased intracranial pressures including altered mental status and high baseline fungal burden, we feel confident in our results [21]. Of note, all study participants; irrespective of sodium level, routinely received at least 154 mmol/L of sodium given as 1 liter of 0.9% intravenous saline before and after amphotericin administration, which may also treat mild to moderate hyponatremia secondary to cerebral salt wasting. In the event that persons with CM present with cerebral salt wasting, receiving normal saline may bias mortality risk towards the null. The reverse would be true for SIADH and other causes of hyponatremia associated with high effective arterial blood volume. This underscores the importance of determining the cause of hyponatremia in future studies.

Conclusion:

In summary, hyponatremia is a common presentation and poor prognostic indicator in HIV associated cryptococcal meningitis. Our findings further suggest that individuals with low sodium levels present with more severe CNS disease. Further studies investigating the pathophysiological mechanism leading to hyponatremia is warranted as optimal supportive therapy to correct hyponatremia may improve outcomes.

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Potential Conflicts of Interest:

There are no conflicts of interest to disclose.

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Table 1: Baseline Characteristics

Baseline Characteristic	Na+ <125 mmol/L		Na+ 125-129 mmol/L		Na+ 130-145 mmol/L		
	N	Median [IQR] or N (%)	N	Median [IQR] or N (%)	N	Median [IQR] or N (%)	P-value[a]
Age, years	121	36 (30,43)	194	35 [30, 42]	426	35 [29, 40]	**0.04**
Men	121	85 (70.2)	194	118 (60.8)	426	240 (56.3)	**0.02**
Receiving HIV therapy	121	68 (56.2)	194	85 (43.8)	426	217 (50.9)	0.08
Glasgow Coma Score < 15	120	63 (52.5)	193	87 (45.1)	422	150 (35.5)	**<0.01**
Seizure	120	29 (24.2)	193	26 (13.5)	422	64 (15.2)	**0.03**
Prior Cryptococcal Meningitis	120	10 (8.3)	194	13 (6.7)	420	21 (5.0)	0.35
CD4, cells/μL	115	21 [6, 43]	184	17 [7, 47]	402	20 [8, 53]	0.45
Hemoglobin, g/dL	120	12 [10, 13]	186	11 [10, 13]	421	11 [10, 13]	0.23
Creatinine, mg/dL	121	0.6 [0.6, 0.8]	193	0.8 [0.6, 0.9]	424	0.7 [0.6, 0.9]	**<0.001**
CSF white cells/μL	119	<5 [<5, 40]	182	<5 [<5, 45]	408	<5 [<5, 55]	0.41
CSF white cells < 5/μL	119	76 (63.9)	182	111 (61.0)	408	234 (57.4)	0.39
CSF protein, mg/dL	100	40 [23, 94]	162	50 [25, 98]	365	74 [37, 118]	**<0.01**
CSF glucose, mg/dL	57	67 [39, 84]	76	47 [33, 86]	254	64 [41, 85]	0.09
Opening pressure, cmH_20	113	27 [18, 38]	173	25 [17, 37]	380	23 [15, 34]	**<0.01**
CSF culture, log_{10} CFU/mL	120	4.8 [4.2, 5.9]	191	4.7 [2.8, 5.4]	415	4.3 [2.4, 5.5]	**<0.001**
CSF removed, mL	118	15 [9, 22]	187	14 [8, 19]	386	12 [8, 18]	0.01

[a] P-value by Kruskal-Wallis or chi-square test.

Table 2. Survival Outcomes by Baseline Serum Sodium Groups

Event		Na+ <125 mmol/L	P-value	Na+ 125-129 mmol/L	P-value	Na+ 130-145 mmol/L
Deaths	N Overall Patients	121		194		426
within 2	N (%) with Death	48 (39.7)		47 (24.2)		72 (16.9)
Weeks	Event Rate (95% CI)[a]	1.10 (0.79, 1.41)		0.62 (0.44, 0.79)		0.41 (0.31, 0.50)
	Hazard Ratio (95% CI)[b]					
	Model 1 - Unadjusted	2.61 (1.81, 3.77)	<.001	1.51 (1.04, 2.17)	0.03	REF
	Model 2 – Adjusted GCS and culture	1.98 (1.34, 2.92)	<.001	1.38 (0.94, 2.01)	0.10	REF
	Model 3	1.87 (1.26, 2.79)	<.01	1.31 (0.89, 1.93)	0.17	REF
Deaths	N Overall Patients	121		194		426
within	N (%) with Event	61 (50.4)		61 (31.4)		97 (22.8)
30 Days	Event Rate (95% CI)[a]	0.78 (0.58, 0.97)		0.41 (0.31, 0.52)		0.27 (0.22, 0.33)
	Hazard Ratio (95% CI)[b]					
	Model 1- Unadjusted	2.62 (1.90, 3.61)	<.001	1.48 (1.07, 2.04)	0.02	REF
	Model 2 - Adjusted GCS and culture	2.07 (1.47, 2.90)	<.001	1.35 (0.97, 1.87)	0.08	REF
	Model 3	1.88 (1.33, 2.66)	<.001	1.24 (0.89, 1.74)	0.21	REF

[a] Rate per 30 person days; [b] Model 1=Unadjusted, Model 2=Adjusted for Glasgow coma scale (GCS) score and CSF quantitative culture, Model 3= Adjusted for GCS, culture, and study cohort. Abbreviations: CI = Confidence Interval, IQR = Interquartile range.

Figure 1: 30-Day Survival by Baseline Serum Sodium Category

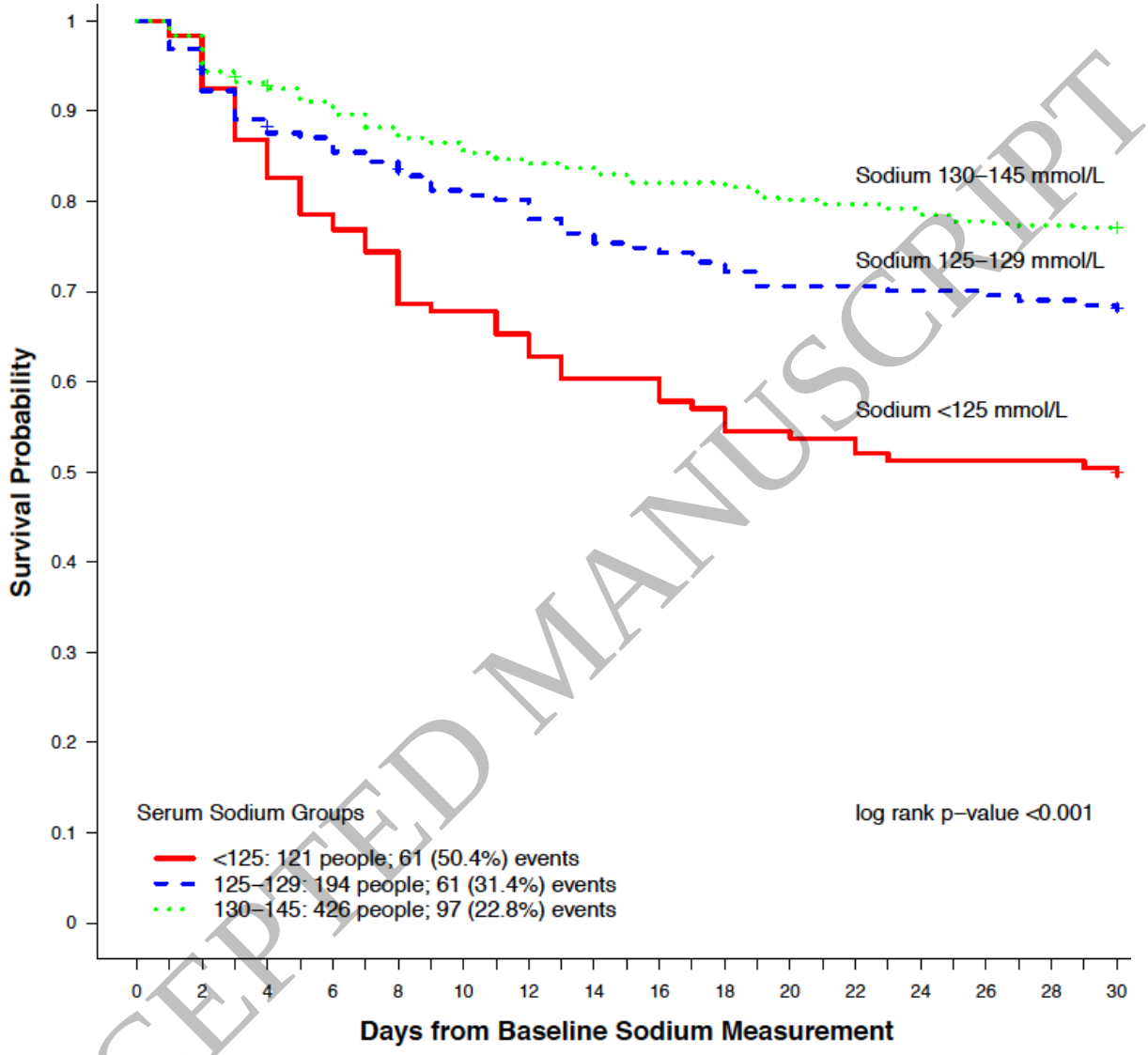
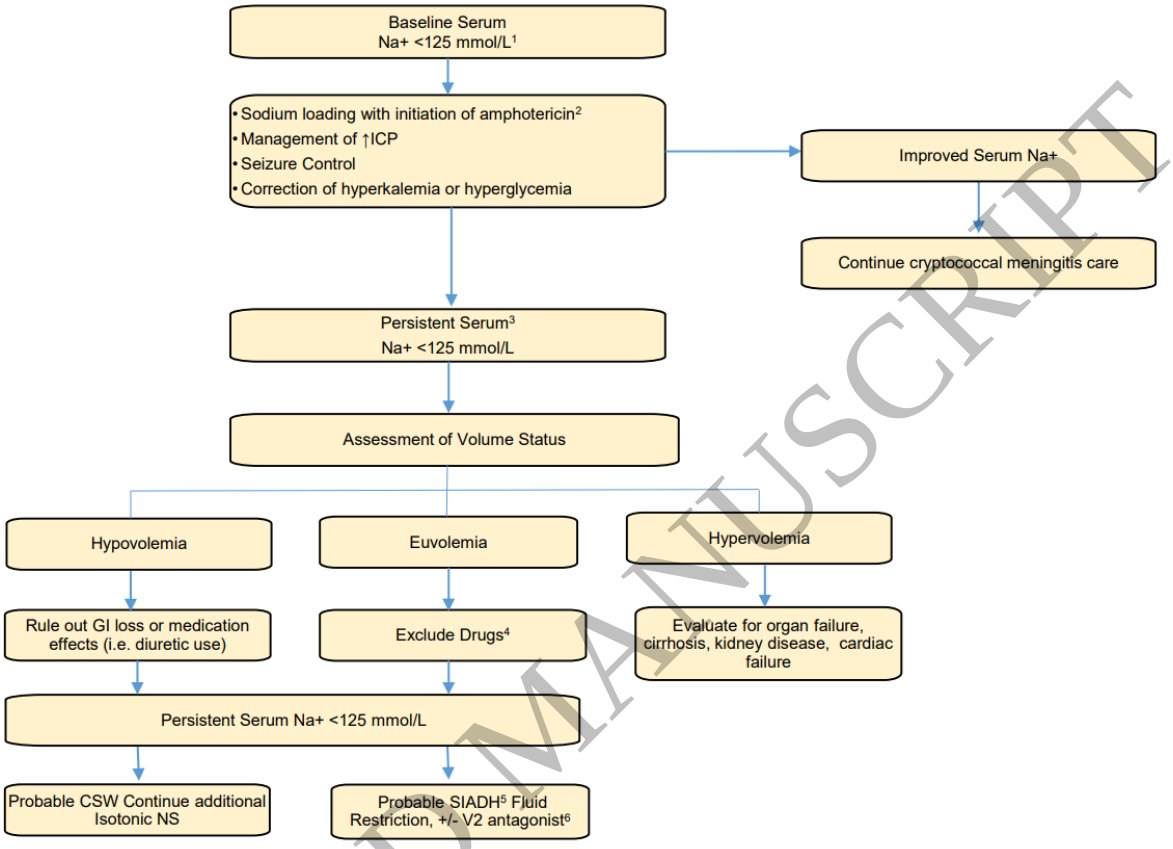


Figure 2: Pragmatic approach to the evaluation and management of severe hyponatremia in adults with HIV associated Cryptococcal Meningitis



[1]Monitoring of serum Na+ recommended daily until stable.
[2]Initiation of amphotericin based antifungal therapy requires administration of normal saline prior to and after infusion. Correction of serum Na+ levels is less urgent in the first 48 hours as patients with chronic hyponatremia are at risk of osmotic demyelination syndrome.
[3]Persistent serum Na+<125 mmol/L by day 7 of cryptococcal meningitis care
[4]Exclude drugs known to enhance activity of arginine vasopressin including carbamazepine.
[5]Patients with SIADH may respond to continued treatment of cryptococcal meningitis.
[6]Vasopressin (V2)-receptor antagonist