Original Article

Hyponatremia in Melioidosis: Analysis of 10-year Data from a Hospital-Based Registry

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Abstract

Introduction: Hyponatremia is a frequent finding in hospitalized patients and is associated with poor clinical outcomes. While hyponatremia is known to commonly occur in certain infections, its association with melioidosis has not been studied previously. We studied incidence and impact of hyponatremia on clinical outcomes in melioidosis. **Methods:** This was a retrospective analysis of a single-center hospital registry of culture-positive patients with melioidosis hospitalized during a 10-year period (January 01, 2010, through January 31, 2021). Hyponatremia was defined as serum sodium of <135 mmol/L, and severe hyponatremia as serum sodium <120 mmol/L. The association of hyponatremia with in-hospital mortality, need for intensive care unit (ICU) stay and mechanical ventilation was studied. **Results:** Of 201 patients with melioidosis, 169 (84.1%) had hyponatremia, with severe hyponatremia in 35 (17.4%) patients. Older age (adjusted odds ratios [OR] 1.03, 95% confidence intervals [CI]: 1.00–1.06; $P = 0.049$) and acute kidney injury (AKI) (adjusted OR 3.30, 95% CI: 1.19-9.19; $P = 0.02$) were independently associated with hyponatremia. Twenty-two patients had been evaluated for cause of hyponatremia and of these, 11 (50%) had syndrome of inappropriate antidiuresis. Severe hyponatremia was associated with in-hospital mortality (adjusted OR 3.75, 95% CI: 1.37–10.27; $P = 0.01$), need for ICU stay (adjusted OR 7.04, 95% CI: 2.88–17.19; $P < 0.001$) and mechanical ventilation (adjusted OR 3.99, 95% CI: 1.54–10.32; $P = 0.004$). **Conclusion:** Hyponatremia occurs in 84.1% of hospitalized patients with melioidosis. Older age and AKI are associated with a higher incidence of hyponatremia. The presence of severe hyponatremia is an independent predictor of in-hospital mortality, need for mechanical ventilation and ICU stay.

Keywords: *Burkholderia pseudomallei*, dysnatremia, electrolyte imbalance, infectious disease

Introduction

Melioidosis, caused by a Gram-negative bacillus *Burkholderia pseudomallei*, is a life-threatening disease endemic to Southeast Asia and Northern Australia. Often called the great mimicker, it may present with manifestations ranging from a chronic localized infection to an acute fulminant infection with multi-organ abscesses and has a high case-fatality rate of 16%–44%.[1,2]

Hyponatremia is frequently encountered in the setting of infection, with a reported incidence of 20%–60%.[3,4] Certain infections such as *Legionella* pneumonia, malaria, tuberculosis, HIV, and most recently, SARS-CoV-2 have been reported to be commonly associated with hyponatremia.[5-9]

Although hyponatremia is often overlooked and under-evaluated, even mildly diminished levels of serum sodium (<135 mmol/L) have been linked with poorer clinical outcomes.[10] Several studies have found that the presence of hyponatremia is an independent risk factor for in-hospital mortality and prolonged duration of hospitalization, both in infectious and other clinical settings.[11-15] Hyponatremia is also associated with an increased need for intensive care unit (ICU) stay and mechanical ventilation.[16]

The association of melioidosis with hyponatremia has not been well described. Moreover, little is known about the

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mechanism of hyponatremia and its effect on clinical outcomes in this setting. In the present study, we sought to determine the incidence of hyponatremia and study its impact on clinical outcomes in hospitalized patients with melioidosis.

Methods

Study design and setting

This was a retrospective analysis of a melioidosis registry at Kasturba Medical College, Manipal, a tertiary care referral hospital in the Udupi district of South India. The incidence of melioidosis in the Udupi district has been estimated to be 0.8/1000 hospital admissions and 1/100,000 population and this hospital has reported the highest number of cases of melioidosis in any single center in India.[17]

The study was approved by the Institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki.

Study participants

Adults (>18 years) with confirmed melioidosis based on positive culture for *B. pseudomallei* from any clinical specimen admitted during a 10-year study (January 01, 2010, through January 31, 2021) were included. Demographic, clinical and laboratory data were collected from hospital medical records. The outcomes studied were in-hospital mortality, need for ICU stay and mechanical ventilation.

Study definitions

A confirmed case of melioidosis was defined as one with a positive culture for *B. pseudomallei* from any clinical specimen. Hyponatremia was defined as serum sodium <135 mmol/L, and severe hyponatremia as serum sodium <120 mmol/L.[18] A diagnosis of syndrome of inappropriate antidiuresis (SIAD) was made if serum osmolality was <280 mOsmol/kg water, with urine osmolality of >100 mOsmol/kg water and urine sodium of >20 mmol/L.[19] Acute kidney injury (AKI) was defined and staged as per the 2012 KDIGO guidelines.[20] The diagnosis of sepsis was based on hospital records.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0. Continuous data were tested for normality using the Kolmogorov–Smirnov test. Categorical data were presented as frequency (*n*) and percentages (%) and normally distributed descriptive data were presented as mean and standard deviation. Comparison of proportions was performed using the Chi-squared test and normally distributed continuous data were compared using the two-sample *t*-test. Univariable and multivariable logistic regression analysis was performed to identify factors associated with hyponatremia and to study the effect of severe hyponatremia on in-hospital mortality, need for ICU care and mechanical ventilation. Crude and adjusted odds ratios were calculated, with 95% confidence intervals (CI). All results were considered statistically significant at a $P < 0.05$.

Results

Patient characteristics

Two hundred and sixteen patients with melioidosis were identified during the study. After excluding those who did not have serum sodium reports, a total of 201 patients were included for analysis. The baseline characteristics are tabulated below in Table 1.

The mean age was 51.5 ± 13.6 years, and 158 (78.6%) were male. Diabetes mellitus, hypertension, and chronic kidney disease were the most common preexisting comorbidities and were seen in 154 (76.6%), 67 (33.3%), and 18 (9.0%), respectively. The most common clinical presentations were pneumonia and skin and soft tissue abscesses in 90 (44.8%) and 53 (26.4%) patients, respectively. Sixty-three patients (31.3%) received ceftazidime, 92 (45.8%) received meropenem and no treatment details were available for the rest.

Hyponatremia in melioidosis

Hyponatremia was seen in 169 (84.1%) patients, with a mean serum sodium of 124.7 ± 6.7 mmol/L. At admission,

Table 1: Clinical characteristics of study population

	Total number (*n*=201)
Age, years (mean±SD)	51.5±13.6
Gender, *n* (%)	
Male	158 (78.6)
Female	43 (21.4)
Co-morbidities, *n* (%)	
Diabetes mellitus	154 (76.6)
Hypertension	67 (33.3)
CKD	18 (9.0)
CLD	8 (4.0)
Malignancy	7 (3.5)
Steroid therapy	4 (2.0)
HIV	2 (1.0)
Clinical presentation	
Pneumonia	90 (44.8)
Skin and soft tissue abscess	53 (26.4)
Liver abscess	12 (6.0)
Splenic abscess	17 (8.5)
Other visceral abscesses	3 (1.5)
Septic arthritis/osteomyelitis	38 (18.9)
Encephalomyelitis	5 (2.5)
Bacteremia	131 (65.2)
Severity of involvement and outcomes	
Sepsis	85 (42.3)
AKI	71 (35.3)
Stage 1	26 (12.9)
Stage 2	22 (10.9)
Stage 3	23 (11.4)[a]
Shock	36 (17.9)
ICU stay	54 (26.9)
Need for mechanical ventilation	33 (16.4)
In-hospital mortality	29 (14.4)

[a]Of those with stage 3 AKI, 17 required dialysis. SD: Standard deviation, CKD: Chronic kidney disease, CLD: Chronic liver disease, HIV: Human immunodeficiency virus, AKI: Acute kidney injury, ICU: Intensive care unit

154 (76.6%) patients had hyponatremia and another 15 (7.5%) developed it during the hospital stay. Severe hyponatremia was noted in 35 (17.4%) patients.

Complete evaluation of hyponatremia, including serum and urine osmolality, urine sodium, serum cortisol, and thyroid function tests had been done in 22 patients, all of whom had serum sodium ≤125 mmol/L. Of these 22, 11 (50%) had features consistent with SIAD.

On comparison of those with and without hyponatremia, those with hyponatremia were older (mean age 52.5 ± 13.5 years vs. 46.1 ± 13.1 years, $P = 0.02$). Hyponatremia was also more common among patients with diabetes mellitus ($P = 0.02$) and AKI ($P = 0.01$) compared to those without. There was no significant difference between the two groups with respect to other covariates. On multivariable logistic regression analysis, age (adjusted OR 1.03, 95% CI: 1.00–1.06; $P = 0.049$), and AKI were independently associated with hyponatremia (adjusted OR 3.30, 95% CI: 1.19–9.19; $P = 0.02$) [Table 2].

Clinical outcomes

Fifty-four patients (26.9%) with melioidosis required intensive care, 33 (16.4%) needed mechanical ventilation and in-hospital mortality occurred in 29 (14.4%).

There was no statistical difference in mortality rates of those with and without hyponatremia (14.8% vs. 12.5%, $P = 1.0$). However, those with severe hyponatremia had a higher mortality rate than those without (28.6% vs. 11.5%, $P = 0.01$). Need for ICU care (57.1% vs. 20.5%, $P < 0.001$) and mechanical ventilation (31.4% vs. 13.3%, $P = 0.01$) was also higher among those with severe hyponatremia.

On multivariable logistic regression analysis, severe hyponatremia was independently associated with in-hospital mortality an adjusted OR of 3.75 (95% CI: 1.37–10.27; $P = 0.01$) [Table 3]. Severe hyponatremia was also associated with need for intensive care with an adjusted OR of 7.04, 95% CI: 2.88–17.19; $P < 0.001$ and mechanical ventilation with adjusted OR of 3.99, 95% CI: 1.54–10.32; $P = 0.004$ [Tables 4 and 5]. Female gender and AKI were also independently associated with adverse clinical outcomes [Tables 3-5].

Table 2: Predictors of hyponatremia in patients with melioidosis

Covariate	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age	1.04 (1.00-1.01)	0.02	1.03 (1.00-1.06)	0.049
Male gender	1.89 (0.82-4.39)	0.14	-	-
Diabetes mellitus	2.51 (1.11-5.66)	0.03	2.16 (0.92-5.07)	0.07
Hypertension	1.54 (0.65-3.66)	0.33	-	-
CKD	0.91 (0.25-3.35)	0.89	-	-
CLD	1.30 (0.15-10.92)	0.81	-	-
Pneumonia	1.63 (0.74-3.62)	0.23	-	-
AKI	3.40 (1.24-9.29)	0.02	3.30 (1.19-9.19)	0.02

CKD: Chronic kidney disease, CLD: Chronic liver disease, AKI: Acute kidney injury, OR: Odds ratio, CI: Confidence interval

Table 3: Predictors of in-hospital mortality in melioidosis

Covariate	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age	1.01 (0.98-1.04)	0.36	-	-
Male gender	0.47 (0.20-1.15)	0.09	0.24 (0.08-0.61)	0.004
Diabetes mellitus	0.89 (0.37-2.35)	0.89	-	-
Hypertension	1.48 (0.66-3.30)	0.34	-	-
CKD	0.71 (0.16-3.28)	0.66	-	-
CLD	3.81 (0.86-16.89)	0.08	3.08 (0.56-17.04)	0.20
AKI	7.63 (3.06-19.02)	<0.001	9.48 (3.47-25.93)	<0.001
Severe hyponatremia	3.05 (1.27-7.33)	0.01	3.75 (1.37-10.27)	0.01

CKD: Chronic kidney disease, CLD: Chronic liver disease, AKI: Acute kidney injury, OR: Odds ratio, CI: Confidence interval

Discussion

We found hyponatremia in 84.1% of patients hospitalized with melioidosis, and severe hyponatremia in 17.4%. Of these, most patients (76.6%) had hyponatremia at presentation.

There is scarce literature on hyponatremia in the setting of melioidosis. In fact, data on serum sodium levels are not available in most studies on melioidosis and this clinical finding may have been hitherto overlooked. A few retrospective studies have alluded to hyponatremia as a finding in as high as 90% of patients with melioidosis; however, these studies did not specifically focus on this issue.[21,22] Similarly, a few case reports and one case series of melioidosis have mentioned hyponatremia as a finding.[23-25]

The pathophysiological mechanisms underlying hyponatremia in melioidosis are unclear. Li *et al*., in a case report of a patient with melioidosis-associated mycotic aneurysm, mentioned hyponatremia consistent with SIAD as a finding.[23] We found evidence of SIAD in 50% of the patients evaluated for hyponatremia. While SIAD could be the predominant cause of hyponatremia among other patients as well, it is not possible to determine the exact etiology in the absence of further data.

In the majority of patients with infections, hyponatremia is believed to be caused by increased antidiuretic hormone (ADH) secretion, either appropriately or inappropriately.[3,26] While nonosmotic stimuli such as hypovolemia, nausea, pain and certain medications could increase ADH secretion, the possible role of interleukin (IL)-6 or cytokine-mediated ADH release has also been postulated.[26,27] Another proposed mechanism is that of a reset osmostat due to changes in arterial partial pressure of carbon dioxide and oxygenation.[28] There is also evidence which suggest increased levels of atrial natriuretic peptide, as well as B-type-natriuretic peptide in patients with pneumonia.[29,30] These hormones may contribute to low sodium levels through increased natriuresis. Moreover, increased cytokine levels could also directly induce renal salt loss.[31,32]

Acute interstitial nephritis (AIN) causing renal salt wasting has been described as a cause of hyponatremia in legionellosis.[33] This mechanism is of particular interest since AIN has been

Table 4: Predictors of need for intensive care unit care in melioidosis

Covariate	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age	1.03 (1.00-1.05)	0.04	1.01 (0.98-1.04)	0.68
Male gender	0.33 (0.17-0.68)	0.002	0.18 (0.08-0.41)	<0.001
Diabetes mellitus	0.80 (0.39-1.65)	0.55	-	-
Hypertension	1.72 (0.90-3.28)	0.09	1.40 (0.65-3.02)	0.38
CKD	1.83 (0.67-4.99)	0.24	-	-
CLD	1.66 (0.38-7.19)	0.50	-	-
AKI	2.96 (1.55-5.67)	0.001	3.82 (1.80-8.12)	<0.001
Severe hyponatremia	5.14 (2.38-1.08)	<0.001	7.04 (2.88-17.19)	<0.001

CKD: Chronic kidney disease, CLD: Chronic liver disease, AKI: Acute kidney injury, OR: Odds ratio, CI: Confidence interval

Table 5: Predictors of need for mechanical ventilation in melioidosis

Covariate	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age	1.02 (0.99-1.05)	0.11	-	-
Male gender	0.33 (0.19-0.93)	0.03	0.21 (0.08-0.53)	0.001
Diabetes mellitus	0.79 (0.46-2.80)	0.79	-	-
Hypertension	1.36 (0.63-2.94)	0.43	-	-
CKD	0.28 (0.04-2.15)	0.22	-	-
CLD	3.24 (0.74-14.28)	0.12	-	-
AKI	5.25 (2.32-11.91)	<0.001	6.78 (2.74-16.78)	<0.001
Severe hyponatremia	2.98 (1.28-6.92)	0.01	3.99 (1.54-10.32)	0.004

CKD: Chronic kidney disease, CLD: Chronic liver disease, AKI: Acute kidney injury, OR: Odds ratio, CI: Confidence interval

reported in patients with melioidosis as well.[21] We found that AKI occurred in over a third of patients with melioidosis and hyponatremia was three times more likely to occur in those with AKI. However, the etiology of renal dysfunction in our cohort was unknown since histopathological data was lacking.

Although there are several plausible explanations for hyponatremia in infections, it is unlikely that a single mechanism underlies all cases. Hypervolemic hyponatremia attributable to heart failure, cirrhosis, and renal failure, and hypovolemic hyponatremia due to gastrointestinal loss and diabetic ketoacidosis could all account for the derangements in serum sodium levels.

Further, we also found that patients with melioidosis and severe hyponatremia were approximately four times more likely to die in-hospital and need mechanical ventilation, and seven times more likely to require intensive care. This is consistent with previous studies in hospitalized patients which found that irrespective of the etiology of hyponatremia, low serum sodium levels are associated with poor clinical outcomes.[11-15] Waikar *et al*., in a large prospective study, found that serum sodium levels <135 mmol/L at the time of hospital admission was independently associated with an increase of in-hospital mortality by 47%.[13] In addition, the presence of hyponatremia at admission has been associated with prolonged hospitalization.[34,35] In the setting of infectious diseases too, the association of hyponatremia with poorer outcomes has been reported.[36,37] However, whether this association indicates a causal relationship between hyponatremia and disease outcomes, or if hyponatremia simply reflects the severity of the underlying disease is unclear.

Our study also draws attention to the fact that hyponatremia in patients with melioidosis is often under-evaluated. Even in those with severe hyponatremia, only 40% (14/35) had been evaluated for the cause in our cohort. This is a significant concern since the identification of the underlying cause of hyponatremia has important therapeutic implications. While free water restriction is necessary for patients with SIAD, those with sepsis would clearly benefit from fluid resuscitation. Moreover, studies show that the failure to adequately investigate and treat hyponatremia, especially in those with severe hyponatremia, has been associated with adverse outcomes.[38,39] Huda *et al.* reported that only about 25% of patients of patients with serum sodium of < 125 mmol/L had undergone tests for serum and urine osmolality, while urine sodium had only been measured in 10%.[38] They also found that inappropriate management of hyponatremia, in terms of inadequate investigation or incorrect treatment, was associated with higher in-hospital mortality.

Our study has several strengths. It includes a large cohort of patients admitted over a 10-year study period with melioidosis and, to the best of our knowledge, is the first to specifically examine the incidence of hyponatremia, its risk factors, and its impact on outcomes in this setting. A major drawback is that this being a retrospective study, there is a paucity of data on serum and urine osmolality, urine electrolytes, patients' volume status at presentation, and details regarding the use of medications such as diuretics. Although limited by the lack of etiological data, this study highlights the finding that hyponatremia is exceedingly common and that severe hyponatremia is an adverse prognostic indicator among patients hospitalized with melioidosis. The potential utility of serum sodium levels as a diagnostic clue for melioidosis needs to be explored. The mechanism of hyponatremia in melioidosis remains mostly elusive and needs to be studied further.

Conclusion

Hyponatremia occurs in a majority of hospitalized patients with melioidosis, with an incidence of 84.1% in our study. While the exact etiology is unclear in most, a subset of patients has features of SIAD. The presence of severe hyponatremia is associated with poor clinical outcomes.

Research quality and ethics statement

The authors of this manuscript declare that this scientific work complies with reporting quality, formatting and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was approved by the Institutional Ethics Committee (IEC no. 601).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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