

Hyponatremia and Mortality: How Innocent is the Bystander?

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For those who are not electrolyte enthusiasts, hyponatremia can be a frustrating disorder. Dealing with hyponatremia means considering various and often opposite scenarios. Does the patient have hypovolemic, euvolemic, or hypervolemic hyponatremia? Is it acute or chronic? Symptomatic or asymptomatic? Do I want to correct rapidly or more slowly? Shall I give normal saline, hypertonic saline, or water restriction? And—every resident's nightmare—which of the impossible formulas shall I use to calculate the correction rate? These challenges may be the reason that the management of hyponatremia is still suboptimal (1–3). This is worrisome not only because hyponatremia counts as the most common electrolyte disorder in hospitalized patients but also because it is associated with increased mortality. The association between hyponatremia and mortality has been demonstrated in numerous studies (4–9), but causality has been difficult to prove. Therefore, two possibilities remain (Figure 1): (1) Hyponatremia is a direct cause of death, or (2) severe underlying disease is the cause of death and hyponatremia is merely another complication of this underlying disease.

In this issue, Chawla *et al.* (10) elegantly rephrase the issue of hyponatremia and mortality as, “Do patients die with or from hyponatremia?” The investigators first show mortality rates in a large sample of hospitalized patients with hyponatremia (serum sodium <135 mmol/L). Similar to previous observations (9), mortality rose as serum sodium dropped. Surprising, however, this trend reversed when serum sodium reached values of ≤ 120 mmol/L, when mortality rates started to decrease again. The final result was a parabolic relationship between serum sodium and mortality. On the basis of these observations, Chawla *et al.* formulate an interesting hypothesis (10): That patients with moderate hyponatremia have more severe underlying disease than those with severe hyponatremia and therefore higher mortality rates. The patients with severe hyponatremia, they argue, were likely admitted because their serum sodium was so low, not because they were so ill.

In the remainder of the article, the authors seek to confirm this hypothesis by performing a detailed chart review of 53 fatal cases with serum sodium <120 mmol/L and 35 survivors with serum sodium <110 mmol/L. Indeed, the authors note that more

than half of the fatal cases had severe conditions associated with high mortality rates, including sepsis and acute kidney injury. These disorders were largely absent in survivors, whose more severe hyponatremia was largely attributed to the use of thiazides and antidepressants. Importantly, hyponatremia's most dangerous and potentially fatal complications, cerebral edema and the osmotic demyelination syndrome, were rarely observed. Thus, the authors conclude that patients die with and not from hyponatremia. This is an interesting conclusion that will definitely stir debate on the value of actively treating hyponatremia. The study is also an interesting example of how detailed chart reviews sometimes provide more clinical insight than sophisticated statistics.

Two limitations of the study, however, should be noted. First, the study was retrospective, and, therefore, the quality of the information was dependent on the quality of the charts. Second, the groups of “survivors” and “deaths” were not ideal for comparison because they differed in not one but two crucial aspects (different serum sodium cutoff and different outcome). Instead, it would have been better to compare all patients who had a serum sodium concentration of 110 to 120 mmol/L with all patients who had a serum sodium concentration <110 mmol/L. If patients with a serum sodium between 110 and 120 mmol/L would have had more comorbidity than the group with a serum sodium <110 mmol/L, then this would have made a stronger case for the authors' hypothesis.

Does this study prove hyponatremia to be an innocent bystander in mortality? Not entirely. The nuance comes from a third possibility (Figure 1): Hyponatremia may contribute to organ dysfunction and therefore indirectly contribute to mortality. For example, emerging data implicate hyponatremia in falls (11), osteoporosis (12), and fractures (13–15), suggesting an effect on the nervous system and bone. Little is known about the effects of hyponatremia on other organs, such as the heart, although a recent study identified hyponatremia as an independent predictor of myocardial infarction in community patients (16). More is known about the metabolic adverse effects of *hyponatremia*, which can aggravate peripheral insulin resistance (17), impair hepatic gluconeogenesis (18), and induce a negative inotropic response (19). Thus,

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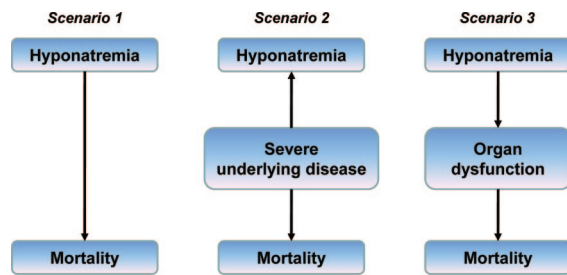


Figure 1. | Three scenarios illustrate the possible relationships between hyponatremia and mortality. In the first scenario, hyponatremia is a direct cause of death. Examples include hyponatremia leading to cerebral edema in acute hyponatremia and the osmotic demyelination syndrome when chronic hyponatremia is corrected too rapidly. In the second scenario, the severity of the underlying disease is the cause of death and also the cause of hyponatremia. In this scenario, hyponatremia does not contribute to mortality but is merely an epiphenomenon of the underlying disease. In the third scenario, hyponatremia causes organ dysfunction and therefore indirectly contributes to mortality.

precise physiologic studies in patients with hyponatremia are warranted to assess better its possible contribution to organ dysfunction. This third possibility may also explain why hyponatremia has been identified as an independent predictor of mortality in several studies (7–9,14,16). This independent relationship has even been established in community patients with mild hyponatremia (15,16), in whom acute underlying disease, cerebral edema, and osmotic demyelination are less likely causes of death. It is important to note that the three possible relationships between hyponatremia and mortality (Figure 1) are not mutually exclusive. Although rare, cerebral edema and osmotic demyelination remain potential causes of death in any patient with hyponatremia (scenario 1). Likewise, hyponatremia is a marker of poor prognosis in advanced liver cirrhosis (20) and heart failure (21) but probably does not directly contribute to this outcome (scenario 2).

Still, the real question is whether the high mortality rates in patients with hyponatremia represent a fixed epidemiologic law or can be reduced with specific maneuvers. Some have shown better outcomes with rapid correction rates (22), whereas others have found this to be associated with excess neurologic damage (23). The “correction rate debate” has somewhat settled on experts’ consensus of a limit of 10 to 12 mmol/L per d, in which initial rates may be faster if hyponatremia is certain to be acute, and rates should be slower if hyponatremia is likely chronic (24). Perhaps it is not so much the optimal correction rate that is key to better outcomes but rather the prevention of hyponatremia. Similar to intensive glycemic control, one could envisage randomly assigning patients to “intensive natriuretic control” or standard care to determine whether this would reduce mortality rates. This would not mean more aggressive treatment but more aggressive monitoring and earlier intervention when required. Because hyponatremia is often acquired or aggravated in hospital (3,6), there is a lot to win. The challenge, of course, is the heterogeneity of hyponatremia. Whereas more insulin will nearly always lower serum glucose, effective intervention for hyponatremia requires knowing its cause. Therefore, in whatever

grand ideas we come up with to tackle mortality in hyponatremia, it will always remain necessary to tailor therapy for the patient with hyponatremia. Alas for the nonenthusiasts: No cookbook medicine for hyponatremia.

Disclosures

None.

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See related article, "Mortality and the Serum Sodium: Do Patients Die from or with Hyponatremia?" on pages 960–965.