Sodium, the most abundant extracellular electrolyte, is critical to maintaining serum osmolality and tonicity. Hypernatremia, defined as serum sodium >145 mmol/L, is overshadowed in the literature by the more prevalent hyponatremia. Despite this, hypernatremia is a clinically important and commonly encountered problem, particularly in hospitalized people (1). Hypernatremia reflects an imbalance between extracellular water (too little, in relative or absolute terms) and sodium (too much, in relative or absolute terms), most frequently resulting from a combination of excess loss of water or hypotonic fluid with insufficient compensatory intake. In hospitalized people, hypernatremia may exist at presentation, referred to as community-acquired hypernatremia, or develop during the course of hospitalization, known as hospital-acquired hypernatremia. Excess hypotonic fluid losses from febrile illness, heat exposure, gastrointestinal losses, or urinary losses, combined with inability to increase water intake to compensate, drives much community-acquired hypernatremia. Hospital-acquired hypernatremia often results from the same causes, with therapeutic measures sometimes inadvertently augmenting water loss.

Community-acquired hypernatremia is a particular risk to older adults, who may be less able to cope with increased water or hypotonic fluid losses from any stressor due to limited mobility, impaired thirst mechanisms, and limited urine concentrating ability. Hypernatremia (or dysnatremias more broadly) necessarily reflect failures of fundamental homeostatic physiologic responses to match up with stressors or perturbations, and thus portend high risk of adverse outcomes in many clinical situations. Improved understanding of the epidemiology and outcomes of community-acquired hypernatremia may help to prevent or improve some of these adverse outcomes.

In this issue of Kidney360, Arzhan and colleagues investigate the relationship between community-acquired hypernatremia and hospitalization outcomes, with a focus on how outcomes vary with age and kidney function (2). This was a large observational study, leveraging the Cerner Health Facts Database—a database housing deidentified health records from hospitals across the United States. The authors identified 1.9 million adult hospitalizations from 2000 to 2018 in which a serum sodium concentration (Na) measured within 24 hours of admission was either elevated (Na >145 mEq/L) or normal (Na 135–145 mEq/L). Of this cohort, 60,614 people (3%) had hypernatremia at presentation. These hypernatremic people were older and had lower kidney function at presentation. They also disproportionately suffered from acute infectious illness: 12% of hypernatremic patients were hospitalized for urinary tract infection (compared with 6% of normonatremic patients) and 11% were hospitalized for pneumonia (compared with 6% of normonatremic patients). Sepsis was the leading diagnosis in 11% of the hypernatremia group compared with 4% of the normonatremic group. Hospitalization outcomes were markedly worse for the hypernatremic group: odds of mortality were more than 30-fold higher, after adjustment for demographic factors and chronic comorbidities (2). People with hypernatremia were also much more likely to be discharged to hospice care (odds more than 20-fold greater) or to nursing facilities (odds more than 10-fold greater). Risks were highest in the severely hypernatremic, those with Na >155 mEq/L. There was a statistically significant interaction between admission eGFR and hypernatremia, with hospital outcomes markedly worsening with both low admission eGFR and hypernatremia, compared with hypernatremia alone. Older age groups also had markedly worse hospital outcomes with hypernatremia compared with younger age groups.

This study increases our understanding of the complex relationships between community-acquired hypernatremia and specific hospital-based outcomes, including discharge disposition. Arzhan and colleagues explicate the complexity and uncertainty necessarily surrounding the associations between hypernatremia and adverse outcomes, with numerous residual confounding factors, particularly severity of acute illness. Nevertheless, it seems likely that hypernatremia itself plays a causal role in some adverse outcomes and is not solely a bystander marker of illness severity, general homeostatic dysregulation, or volume depletion. There are several different lines of evidence to support this causal importance of Na and extracellular osmolality to health outcomes. Ultimately, if avoiding hypernatremia were not crucial to functioning, we and other animals would not have evolved and maintained such exquisite thirst mechanisms (3). At the cellular level, hyperosmolality and hypertonicity wreak havoc, causing cellular shrinkage, DNA damage, mitochondrial dysfunction, transcriptional inhibition, and apoptosis (4). At the clinical level,
however, it is challenging and often impossible to disentangle the effects of hypernatremia from the effects of the processes that enabled hypernatremia. Nevertheless, progress is being made in understanding the clinical effects of hypernatremia. As one example, hypernatremia has been linked with the persistent inflammation, immunosuppression, and catabolism syndrome observed in critical illness (5), possibly through activating T<sub>H</sub>17 cells to release proinflammatory cytokines, and through direct toxicity to the endothelial glycocalyx (6,7).

Despite uncertainty about the proportion of blame hypernatremia itself has for the observed outcomes, the study by Arzhan et al. provides additional evidence for the importance of optimizing in-hospital management of hypernatremia. Given the complexity of illness in people being hospitalized with hypernatremia, treatment of the hypernatremia itself may be inadvertently neglected. In a large review of hospitalizations in Switzerland, 32% of patients with community-acquired hypernatremia were found to have been given no hypernatremia treatment within the first 4 days of admission (8). The optimal treatment, particularly rate of correction, for community-acquired hypernatremia is uncertain. Concern about adverse effects of rapid correction has led some to extrapolate limits on rates of increase in Na in chronic hypernatremia to set symmetric maximum rates of Na decrease for hypernatremia (9). A careful study investigating outcomes of community-acquired hypernatremia in critically ill people, however, found no difference in outcomes on the basis of rate of correction (10). Presently, the optimal treatment goals for community-acquired hypernatremia are uncertain (9).

Intervening on these high-risk patients has the potential to interrupt the development of complications and potentially curb some of the negative outcomes associated with hypernatremia. Arzhan and colleagues are commended for their contribution to the growing knowledge about the high prevalence and prognostic importance of community-acquired hypernatremia in hospitalized people, and we hope this leads to prospective research into optimal methods to improve outcomes.

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See related article, “Hypernatremia in Hospitalized Patients: A Large Population-Based Study,” on pages 1144–1157.