Shining Renewed Light on a Tried-and-True Test

The Critical Role of Osmolality in Improving Health and Economic Outcomes in Patients with Hyponatremia

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Abstract

Hyponatremia is an important medical and economic problem that is pronounced in diverse patient populations. The common electrolyte disorder is associated with poor clinical outcomes, including high mortality and increased length of stay, which translate into excess resource utilization and costs. Measurement of osmolality is the first step in determining the etiology of hyponatremia. Management of hyponatremia remains suboptimal and critical testing is not routine despite published guidance on diagnosis of the condition, clear associations with poor outcomes, increased medical costs, and significant evidence that correction improves outcomes. Osmolality is a highly cost-effective test that is proven and medically necessary in the management of hyponatremia. Addressing underutilization of the low-cost test, including education on its interpretation, would grant physicians critical information they need to mitigate unfavorable outcomes and enable hospitals to recover a significant portion of the $1.14 billion in potentially avoidable costs associated with electrolyte disorders in the U.S. alone.

Key Statistics

- Hyponatremia occurs in up to **30%** of hospitalized patients[1]
- **47%** increased risk of death in-hospital at 1 year associated with hyponatremia[2]
- Increase of **2 days** in mean length of stay associated with hyponatremia[3]
- Increase of **~50%** in the odds of having a 30-day unplanned readmission or death associated with hyponatremia[4]
- Reduction in overall mortality of **60%** with hyponatremia correction[5]
- **$1.14 billion** in potentially avoidable costs associated with electrolyte disorders in the U.S.[6]
- Osmolality and sodium measured in only **23%** of patients with hyponatremia[7]

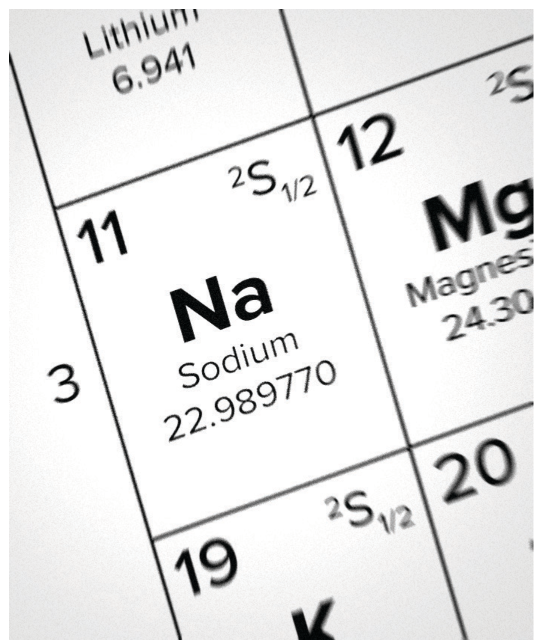
High Incidence & Prevalence of Hyponatremia in Diverse Patient Populations

Hyponatremia, defined as a serum sodium concentration of ≤135 mEq/L, is the most common electrolyte disorder encountered in clinical practice, occurring in up to 30% of hospitalized patients.[1] The prevalence of hyponatremia is conservatively estimated to range from 3.2 million to 6.1 million people in the U.S. on an annual basis. Most patients treated for hyponatremia are initially treated as inpatients (55%–63%), 25% are initially treated in the emergency room, and 13%–20% are exclusively treated in the office setting. In the U.S., there are approximately 1 million hospitalizations per year with a primary or secondary diagnosis of hyponatremia. Additionally, there are an estimated 105,000 to 120,000 annual ER visits, and 1.4 million to 3.4 million annual office visits for hyponatremia.[8]

Hyponatremia is often observed at admission but also frequently develops during hospitalization either as a complication of an underlying illness or as the result of therapeutic interventions.[9] High incidences of hyponatremia have been reported in a variety of patient populations including those with heart failure[10,11], renal disease[12,13], cirrhosis[14], cancer[15,16,17], pneumonia[18], and stroke[19,20]. Hyponatremia also frequently occurs after various surgical procedures including pelvic[21], spinal[22], and pituitary surgery[23,24]. It is particularly prevalent in the elderly, in part because of age-related decline in renal function.[25,26] Additionally, patients who receive maintenance intravenous fluids, particularly children, are in danger of developing hyponatremia.[27,28] Hyponatremia is also common with COVID-19, occurring in nearly a third of hospitalized patients.[29,30]

Association of Hyponatremia with Poor Outcomes

Numerous studies have demonstrated the association between hyponatremia and poor outcomes across diverse patient populations.[31,32,33,34] Winzeler et al. conducted a prospective observational 12-month follow-up study of 281 patients with profound hyponatremia (<125 mmol/L); during the follow-up period, 20.6% of patients died, 56.2% were rehospitalized at least once, and 42.7% had recurrent hyponatremia.[31] However, it is not just severe hyponatremia that has been associated with adverse outcomes. Both mild (130-135 mmol/L) and moderate (125-129 mmol/L) hyponatremia have also been associated with unfavorable outcomes in the literature.[2,35] In a meta-analysis of 81 published studies encompassing 850,222 patients, Corona et al. demonstrated that moderate hyponatremia is associated with an increased risk of mortality, and that it is a negative prognostic factor across multiple commonly observed clinical conditions, such as myocardial infarction, heart failure, cirrhosis, and pulmonary infections.[35] Waikar et al. investigated in-hospital, 1-year and 5-year mortality in a prospective cohort study of 98,411 hospitalized adults and found that patients with hyponatremia had an increased risk of death in-hospital at 1 year (47%) and 5 years (25%). The increased risk of death was evident even in those with mild hyponatremia (37%) and was pronounced in patients admitted with cardiovascular disease, metastatic cancer, and those admitted for procedures related to the musculoskeletal system.[2]



Poor outcomes have also been reported in COVID patients with hyponatremia of varying severity levels.[29,36] In a retrospective, multicenter, observational cohort study, Frontera et al. identified the impact of mild, moderate, and severe admission hyponatremia on outcomes among COVID patients and reported that each level of worsening hyponatremia conferred 43% increased odds of in-hospital death. Further, the authors observed that hyponatremia was an independent predictor of in-hospital mortality and was associated with increased risk of encephalopathy and mechanical ventilation.[29] Similarly, Carvalho et al. conducted a retrospective study of 296 adult patients with a diagnosis of COVID-19 and reported that ICU admission, mechanical ventilation and death were significantly more frequent in hyponatremic patients compared to normonatremic patients (37% versus 14%; 17% versus 6%; 18% versus 9%).[36]

High Resource Utilization & Increased Costs Due to Hyponatremia

Adverse outcomes associated with hyponatremia translate to increased resource utilization due to prolonged length of stay and higher risk of readmission.[3,8,37,38] Balling et al. reported that 1-year mortality was higher for hyponatremic patients (27.5%) versus patients with normal sodium (17.7%) in 2,960 hospitalized adult patients and found that patients with hyponatremia had significantly longer hospitalizations than patients with normal sodium: 7.6 days versus 5.6 days.[3] In a meta-analysis based on 46 published studies encompassing 3,940,042 patients, Corona et al. observed that hyponatremia was associated with a significantly longer duration of hospitalization (3.3 days) and a higher risk of readmission.[37] Similarly, Kutz et al. conducted a population-based cohort study of 94,352 patients and found that hyponatremia patients were 43% more likely to be admitted to the ICU, faced a 56% increase in prolonged length of stay, and were admitted more often to a post-acute care facility.[38] The association between hyponatremia with increased resource utilization is clear at the patient level and is even more evident when scaled to the national level. Boscoe et al. estimated that the total number of additional days of hospitalization due to hyponatremia as a comorbid condition ranges from 497,000 to 4.5 million days per year in the U.S.[8]

Not surprisingly, hyponatremia represents a substantial economic burden. A consensus panel of expert physicians conservatively estimated that the direct costs of treating hyponatremia in the U.S. range between $1.6 billion and $3.6 billion on an annual basis. The panel attributed the bulk of the costs to inpatient hospitalization (70%) and subsequent follow-up treatment (15-20%). Further, the expert physicians reported that more than two-thirds of the total cost of illness results from patients who were admitted for other conditions but required an extended length of stay due to hyponatremia. They estimated that the annual costs per hospitalized patient directly attributable to hyponatremia ranges from $1,528 to $3,441, more than twice the cost per patient with normal sodium.[6,8] Similarly, Corona et al. reported that hyponatremia is associated with an increase of hospital costs of up to $3,000 in the U.S.[37] Shea et al. analyzed data from a large U.S. managed care claim database and found an even higher 1-year mean inpatient cost for patients with hyponatremia ($10,636), more than three times higher than the estimate published by Corona et al.[39]

Hyponatremia Correction Improves Outcomes & Resource Utilization

An abundance of evidence suggests a significant association between hyponatremia correction and improved outcomes across various patient populations.[4,5,31,40] In a large, retrospective cohort study of patients with cancer and severe hyponatremia, Balachandran et al. reported that overall median survival was 13.6 months in those whose sodium was corrected compared to just 16 days in those who remained hyponatremic.[17] Similarly, Corona et al. found that overall mortality rate was associated with a reduction of up to 60% in patients with improved serum sodium compared to patients with no improvement in a meta-analysis of fifteen studies encompassing 13,816 patients. The authors observed a significant association with reduced mortality rate at 12 months and a similar trend at 36 months indicating that the reduced risk of mortality associated with hyponatremia improvement appears to last during prolonged follow-up. They also reported that the effect of the improvement of hyponatremia on the associated lower risk of mortality increases as a function of the prevalence of patients with a more advanced age, an observation that is of particular importance because hyponatremia occurs more commonly in elderly subjects.[5]

Improved outcomes associated with hyponatremia correction translate to decreased resource utilization due to lower length of stay and risk of readmission. In a large, retrospective cohort study of adult patients admitted with a diagnosis of congestive heart failure, Donzé et al. found that persistent hyponatremia was associated with higher odds (approximately 50%) of having a 30-day unplanned readmission or death compared to patients with hyponatremia correction during hospitalization.[4] In a single-center cohort study of hospitalized adult patients, Chewcharat et al. reported that hyponatremia correction was associated with a statistically significant reduction in length of stay by one day, equivalent to the length of stay for patients without hyponatremia.[40] Similarly, Winzeler et al. reported that correction of hyponatremia was significantly associated with lower mortality, rehospitalization and recurrent profound hyponatremia (<125 mmol/L).[31]

Osmolality is Well-Established in the Clinical Pathway for Hyponatremia

Correction of hyponatremia first requires proper diagnosis. The common electrolyte disorder is classified as hypoosmolar, isoosmolar, or hyperosmolar. Understanding the underlying cause of hyponatremia is important as the treatment options vary widely from fluid resuscitation for hyponatremia driven by volume depletion to volume restriction for hyponatremia driven by SIADH.[41,42] It is important to cast a wide net in the initial workup of hyponatremia because patients may present with minimal information regarding relevant medical conditions or recent triggering events.[43] Interpreting various laboratory parameters, including serum and urine osmolality, is necessary to differentiate between the various causes of hyponatremia and ensure proper patient management.[44]

Criteria for diagnosing hyponatremia is well-established.[1,7,45,46] Meaurement of serum osmolality is the first step in the laboratory diagnosis of hyponatremia, and if the test suggests a hypo-osmolar state, then urine osmolality helps determine whether the ability of the kidneys to dilute urine is intact (**Figure 1**).[43]

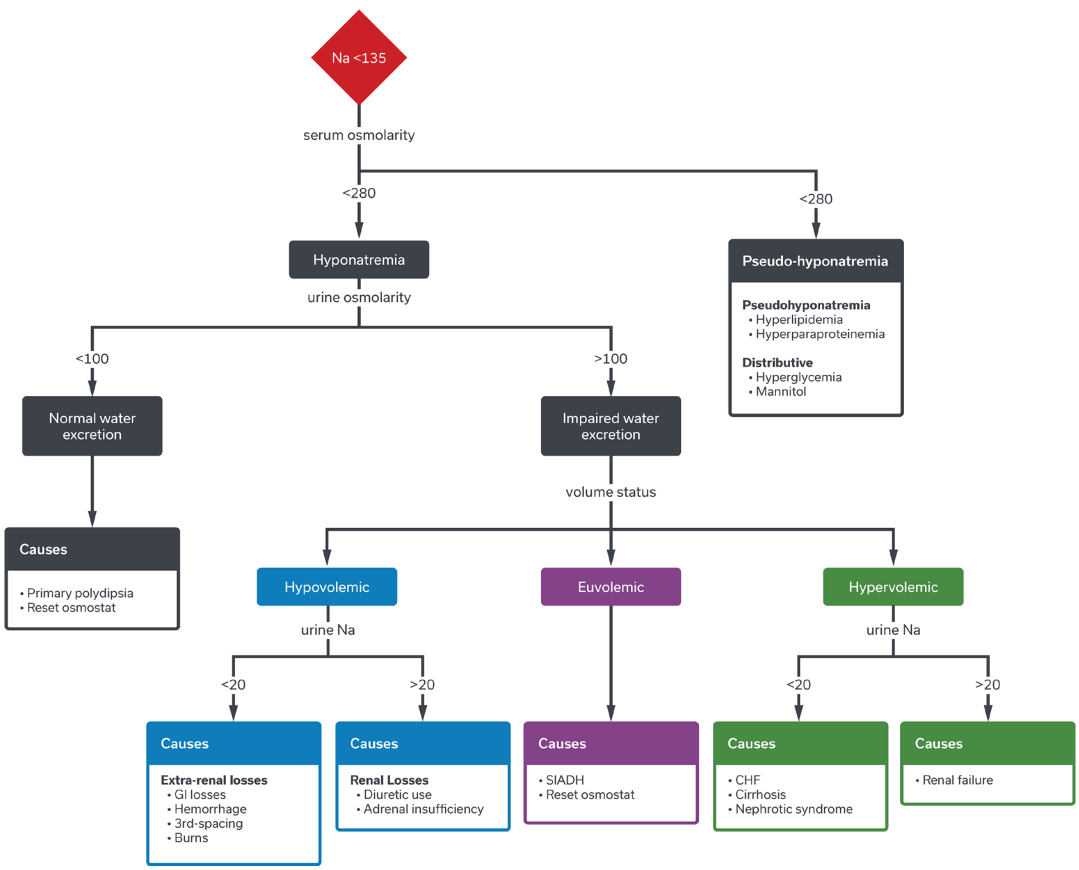


Figure 1. Clinical Pathway for Diagnosing Hyponatremia[43]

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most frequent cause of hyponatremia and the use of serum and urine osmolality to distinguish SIADH from other etiologies is critical. In 1967, Bartter and Schwartz originally defined the diagnostic criteria for SIADH which include measuring serum osmolality, urine osmolality and serum sodium at a minimum and have remained unchanged.[45] More recently, globally recognized expert panels in the U.S. and Europe have published evidence-based guidelines discussing the critical role that serum and urine osmolality measurements play in the classification and differential diagnosis of hyponatremia.[1,7,46] Further, the European expert panel highlighted the increased specificity provided by measured osmolality, which accounts for all osmotically active agents, versus calculated osmolality, which only accounts for osmotically active agents incorporated in the formula.[46]

Most recently, the utility of osmolality has been recognized in the management of COVID patients due to the prevalence of hyponatremia in this patient population.[47,48,49] O'Shea et al. published a COVID test menu for clinical laboratories which includes osmolality testing due to the potential for acute kidney injury in these patients.[47] Similarly, Martinez et al. published guidance recommending daily monitoring of osmolality for inpatients during the acute phase of COVID-19.[48] As of the time of this writing, there are over 350 publications in the National Center for Biotechnology Information (NCBI) electronic database referencing 'osmolality' and 'COVID'.[50]

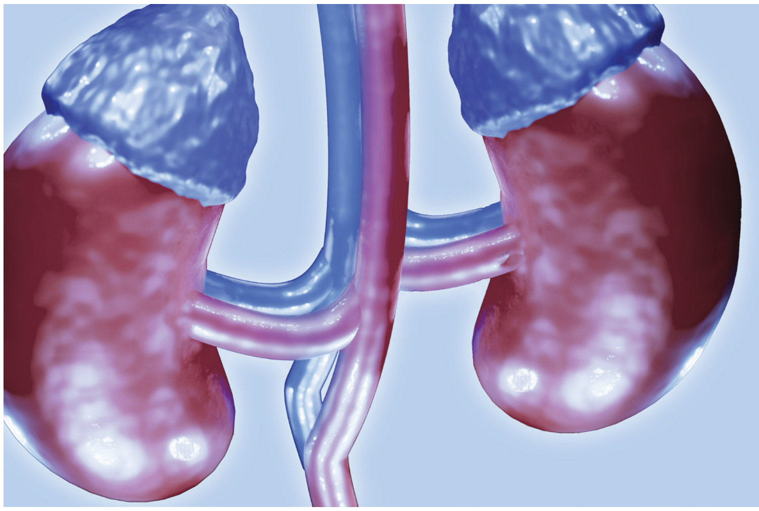
Osmolality Testing is Proven & Medically Necessary for Proper Patient Management

Osmolality is a proven and medically necessary test in the management of hypontremia. Failure to measure plasma and urine osmolality in cases of hypontremia has been associated with increased mortality in the literature.[51,52] In a retrospective study of adult patients with severe hyponatremia, Whyte et al. reported that 30% of patients died when neither serum nor urine osmolality was measured compared to 9.8% when both tests were measured.[51] Similarly, Vaduganathan et al. analyzed serum osmolality measured at discharge in 3,744 patients hospitalized for heart failure and concluded that low discharge serum osmolality was independently predictive of worse discharge mortality and readmission.[52]

Knowledge and interpretation of a patient's osmolality in cases of hyponatremia enables the physician to differentiate between the various causes of the electrolyte disorder and appropriately direct treatment. This is a critical issue because treatment varies drastically based on symptoms and underlying causes. Hyponatremia is treated with fluid restriction (in the setting of euvolemia), isotonic saline (in hypovolemia), and diuresis (in hypervolemia).[53] Lack of osmolality testing makes diagnostic accuracy and subsequent treatment uncertain putting hyponatremic patients at risk.

Underutilization of Osmolality Significantly Impedes Appropriate Management of Hyponatremia

Despite published guidance on its diagnosis, clear associations with poor outcomes and increased medical costs, and significant evidence that correcting hyponatremia is associated with improved outcomes and lower costs, hyponatremia is insufficiently investigated or overlooked entirely, and critical testing is not routine impacting patient treatment.[37,54,55,56]



Inadequate requisition of serum and urine osmolality is frequent in cases of hyponatremia.[7,56] In a multi-center, retrospective, observational study, Tzoulis et al. found that only 23% of patients with hyponatremia had measurements of paired serum and urine osmolality and sodium.[7] The study from Tzoulis et al. is not an outlier; numerous publications in the literature have consistently reported underutilization of measured osmolality in the investigation of hyponatremia.[30,36,57,58,59] Huda et al. evaluated the assessment and management of hyponatremia in a large teaching hospital and found that adequate investigations were rarely performed. In fact, plasma osmolality was measured in only 26% of patients with severe hyponatremia and urine osmolality was measured in only 27%. The authors observed that treatment was often illogical with significant management errors in 33% of cases. Errors included but were not limited to inadequate investigation which could have changed management, treatment with fluid restriction plus intravenous saline, and diuretic induced hyponatremia treated with fluid restriction. Further, mortality was significantly higher in the group with management errors (41% versus 20%). The authors suggest that more appropriate management may have reduced the overall mortality rate. Additionally, they found a trend towards more efficient normalization of serum sodium concentrations in the appropriately managed group, deemed appropriate based on standards for the major diagnostic criteria of hyponatremia.[57] Seo et al. reported similar management errors as Huda et al. The authors highlighted the importance of osmolality test results in guiding therapy.[53]

Even SIADH, the most common cause of hyponatremia, is often diagnosed without attention to the accepted diagnostic criteria.[7,30,58,59] Greenberg et al. conducted an analysis of adult patients in the Hyponatremia Registry from 225 sites in the United States and European Union and observed that only 47% of 1,524 patients with an assigned diagnosis of SIADH had all three cardinal tests (serum osmolality, urine osmolality and serum sodium) performed and 11% had none. Serum osmolality was measured in 66% of patients and urine osmolality in 68%.[58] Burst et al. studied smaller subsets of the Hyponatremia Registry. The authors analyzed 358 cancer patients with a clinical diagnosis of SIADH and similarly found that only 46% of patients had all three tests performed, and 13% had none. They reported that test underutilization was even more pronounced in subgroups including lung cancer patients and small cell lung cancer (SCLC) patients with all tests performed in only 41% and 36% of patients respectively.[59]

Diagnostic rigor appears to be even worse in COVID patients.[30,36,60] In a retrospective, multicenter, observational cohort study of hospitalized patients with laboratory-confirmed SARS-CoV-2, Frontera et al. attempted to determine the etiology of hyponatremia but were unsuccessful because serum and urine osmolality were available in less than 15% of the cohort.[30] Yen et al. reported that serum and urine osmolality measurements were available as part of admission hyponatremia workup tests in only 18% and 12% of cases respectively. Further, the authors reported that serum and urine osmolality were only ordered on the day of admission, when hyponatremia was identified, in 9% and 5.4% of cases respectively.[60] Similarly, Carvalho et al. reported that osmolality was rarely measured in a non-interventional retrospective cohort of patients with mild hyponatremia and COVID-19.[36]

Osmolality is a Cost-Effective Test with a Significant Return on Investment

Not performing osmolality testing is potentially harmful to the patient, but it is also very expensive given that some of the medications now available to treat SIADH cost $500-$1,000 per day. Just one or two misdiagnosed patients can cost the hospital system as much as the price of an osmometer, the device used to measure osmolality. This does not include the possible costs arising from litigation for malpractice due to misdiagnosis and improper treatment.[61] Further, cost per test is highly inexpensive and reimbursement for the test is well-established.[52,62,63]

The College of American Pathologists (CAP) estimated the value generation potential of proper laboratory testing of electrolyte disorders based on Prometheus data and fluid and electrolyte disorders represented 1.5 percent of all potentially avoidable costs. When scaled to the national level and expanded beyond the commercial population based on the CAP's modeling, this represents potential avoidable costs of $1.14 billion nationally.[6] Implementing osmolality testing as standard of care in patients with hyponatremia could help optimize proper patient management to avoid unfavorable outcomes and enable hospitals to recover a significant portion of the $1.14 billion in potentially avoidable costs associated with electrolyte disorders in the U.S.

Multiple Stakeholders Hold the Key to Unlocking the Value of Osmolality Testing

Due to the significant benefits and accrual of cost savings to the hospital, it would reason that utilization of osmolality testing would be higher. However, a problem lies in that both hyponatremia and osmolality testing are not top of mind for all clinicians, particularly those who have not had extensive training on electrolyte disorders. As a result, clinicians may not consider ordering osmolality and they may not be familiar with interpreting the results. For example, by the time a nephrologist gets called for a hyponatremia consult, the patient may have already been in the hospital for several days on intravenous fluids when a simple, affordable osmolality test would have indicated that the patient should, in fact, be fluid restricted.[64]

In a large retrospective cohort study of hyponatremic adult patients admitted to the hospital with a diagnosis of congestive heart failure, Donzé et al. reported that 42% of patients still had hyponatremia at discharge highlighting a lack of recognition of the association of hyponatremia with unfavorable outcomes and resource utilization.[4] Giuliani et al. conducted a survey of physicians (endocrinologists, nephrologists, internists) to investigate the awareness and management of hyponatremia and concluded that there is urgent need for education programs to improve the management of this condition and reduce morbidity, mortality, and costs.[65] Similarly, Huda et al. reported that there is an urgent need for the use of investigative protocols and management pathways in patients with hyponatremia.[57]

Introduction of electronic alerts and order sets for hyponatremia should be considered and tested by hospital quality committees as an opportunity to improve clinical practice. EHR-integrated applications, like AgileMD, enable implementation of clinical pathways into actionable workflows inside of Epic Systems and Cerner to help providers diagnose, manage, and treat patients. The electronic health system could alert the clinician to low sodium levels with suggestions for serum and urine osmolality testing. Based on the results, decision support algorithms for the etiology of the disorder could be offered.[6,7] Teaching hospitals, where clinicians are actively learning about hyponatremia, are an ideal location for alert and order set implementation. Community hospitals would also benefit from alerts and order sets reinforcing when to order osmolality and how to interpret results.

When clinicians have a clear understanding of the importance of determining the etiology of hyponatremia, and the utility of measuring osmolality to do so, it follows that they would be more likely to order the test. However, not all clinical laboratories have an osmometer on-site despite the low cost per test, categorization of osmolality as an ‘urgent’ test, and availability of osmometers for over half a century.[66] The lab may not offer osmolality testing in-house because clinicians are not ordering the test, and clinicians may not order the test because the lab does not have an on-site osmometer which delays results. The cycle is a viscous one and requires partnership between physicians and the lab to bring osmolality testing in-house and help ensure accurate and expeditious patient treatment. Additionally, it may be beneficial for clinical labs to consider reflex osmolality testing upon obtaining low serum sodium levels to improve efficiencies and further expedite patient care.

While clinicians, hospital labs, and quality committees can propel proper utilization of osmolality testing at the site level, payers can effectively drive scale by implementing osmolality into medical policies. Doing so would be highly relevant to insurers seeking to improve outcomes and reduce costs and is substantiated by the plethora of evidence cited herein. (**Figure 2**)

Stakeholder	Benefits
Patient	• Improved outcomes (i.e., better prognosis, reduced length of stay) • More effective treatment
Hospital	• Improvement in readmission rate and reduced associated penalty[67] • Increased profit from reduction in costs • Differentiation from other hospitals via better patient experience
Clinician	• Evidence-based decision-making tool to improve patient care • Improved patient outcomes
Laboratory	• Increased efficiencies • Expedited patient care

Figure 2. Osmolality Testing: Key Stakeholders & Benefits

Conclusion

In summary, hyponatremia represents an important medical and economic burden that is prevalent in various patient populations. Despite published guidance on its diagnosis, clear associations with poor outcomes, increased medical costs, and significant evidence that correcting hyponatremia is associated with improved outcomes, the common electrolyte disorder is often inadequately investigated or ignored. Osmolality testing is proven and medically necessary to effectively manage hyponatremia, improving outcomes and reducing excess resource utilization. However, osmolality is underutilized even though the cost per test is low, the test is classified as 'urgent', and osmometers are well-established medical devices.[66] Osmolality testing combined with education on interpreting test results are both critical in addressing suboptimal management of hyponatremia. The return on investment would be substantial due to the low cost per test and $1.14 billion in potentially avoidable costs associated with electrolyte disorders in the U.S. alone. Addressing underutilization of osmolality testing in cases of hyponatremia, including education of ordering providers, is the first step in ensuring that everyone who needs an osmolality test gets one.

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