Hyponatremia in Pneumonia
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Hyponatremia is relatively common in patients admitted with pneumonia, and it is associated with higher disease severity. The precise mechanism is incompletely understood, but the syndrome of inappropriate antidiuretic hormone secretion is felt to play a significant role. Traditional options to manage hyponatremia in such patients are fraught with challenges. The recently approved vasopressin receptor antagonists offer a new option for the management of this challenging condition. Journal of Hospital Medicine 2012;7:S11–S13 © 2012 Society of Hospital Medicine

M.C. is an 82-year-old female resident of a skilled nursing facility with a past medical history of moderate dementia, hypertension, type 2 diabetes, and stage 3 chronic kidney disease (baseline creatinine, 1.4 mg/dL; creatinine clearance, 33 mL/min). Her serum sodium concentration ([Na⁺]) is normal (range, 136–139 mEq/L) at baseline. She is brought to the emergency department with a 2-day history of fever, productive cough, and altered mental status from baseline. She is febrile (38.7°C), has tachycardia (114 bpm), normal blood pressure (128/76 mmHg), and hypoxemia (89% on 2 L). Physical examination suggests euvolemia. Notable laboratory values include: serum [Na⁺], 127 mEq/L; serum potassium, 4.1 mEq/L; blood urea nitrogen, 14 mg/dL; serum creatinine, 1.5 mg/dL; glucose, 110 mg/dL; plasma osmolality, 253 mOsm/kg; urine [Na⁺], 92 mEq/L; and urine osmolality, 480 mOsm/kg. Chest radiography shows a right lower lobe infiltrate with prominent air-bronchograms. The patient is started on intravenous (IV) antibiotics and normal saline (75 mL/hr), and is admitted to the medical service for management of healthcare-associated pneumonia.

**HYponATREMIA AND PNEUMONIA**

The association of hyponatremia with respiratory illness has been recognized for more than 70 years. Winkler and Crankshaw first reported low serum [Na⁺] in patients with pulmonary tuberculosis in 1938. Roughly 25 years later, reports of hyponatremia in patients with pneumonia began to surface in the literature. The prevalence of hyponatremia (serum [Na⁺] <135 mEq/L) is up to 29% of patients with pneumonia. Low serum [Na⁺] is associated with worse outcomes in such patients. In a large retrospective cohort (n = 7965), Zilberberg and colleagues found that pneumonia patients with hyponatremia (serum [Na⁺] <135 mEq/L) had statistically higher rates of intensive care unit (ICU) admission (10.0% vs 6.3%, P < 0.001), mechanical ventilation (3.9% vs 2.3%, P = 0.01), longer ICU (6.3 vs 5.3 days, P = 0.07) and hospital lengths of stay (7.6 vs 7.0 days, P < 0.001), and a trend toward higher hospital mortality (5.4% vs 4.0%, P = 0.1) as compared with those with normal serum [Na⁺]. Hyponatremia is also associated with higher illness severity in a variety of other patient populations. The underlying nature of these associations, however, remains obscure.

The mechanism of hyponatremia in pneumonia is incompletely understood. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is most often implicated. Patients with pneumonia often present with several factors that are associated with nonosmotic stimulation of antidiuretic hormone (ADH), notably inflammatory cytokines such as interleukin-6, stress, nausea, and hypoxemia. Others implicate a reset osmostat, citing evidence for this mechanism in other infectious conditions (ie, tuberculosis and malaria). Patients with pneumonia may also have concomitant hypovolemia due to factors such as inadequate oral intake, systemic vasodilation, and extrarenal sodium losses from vomiting and diarrhea. In contrast to SIADH, hypovolemia is a potent stimulus for appropriate ADH secretion through activation of the carotid baroreceptors.

**CASE STUDY REVISITED**

M.C.’s initial laboratory assessment would suggest SIADH. Additional testing rules out endocrinopathy (thyroid-stimulating hormone, 2.2 mIU/L; AM serum cortisol, 16 µg/dL). After 3 days of normal saline infusion (75 mL/hr) and IV vancomycin, cefepime, and levofloxacin, her serum [Na⁺] has dropped to 125 mEq/L. Her vital signs have normalized and she is now saturating well on ambient air. She remains...
euvoeamic. Notable laboratory values on hospital day 4 include serum $[Na^+]$, 125 mEq/L; serum creatinine, 1.3 mg/dL; plasma osmolality, 261 mOsm/kg; urine $[Na^+]$, 103 mEq/L; urine potassium, 58 mEq/L; and urine osmolality, 518 mOsm/kg. Her provider invokes a diagnosis of SIADH and appropriately discontinues the normal saline. A fluid restriction of 500 mL/day is then instituted based on her average daily urine volume (1.7 L) and urine/plasma electrolyte ratio (electrolyte-free water clearance = urine osmolality × (1 − ([U Na$\pm$ + U K$\pm$]/P Na$\pm$)).$^{14}$ After 48 hours, her serum $[Na^+]$ has improved to 128 mEq/L, yet she notes extreme thirst. A trial of increased dietary salt is offered, but she refuses, stating that her primary care physician has advised her for years to avoid salt due to her condition, yet the majority of options have significant drawbacks. Although fluid restriction has been promoted for years, the level of restriction must generally be significant and ongoing to be effective. A goal intake of <800 mL/day is usually required to maintain the negative water balance necessary to treat hyponatremia and maintain a normal serum $[Na^+]$.$^{16}$ Patients on such a fluid restriction experience thirst, a fundamentally strong impulse that is difficult to manage. As a result, long-term compliance is extremely challenging.$^{17–19}$ Diets high in solute (sodium and/or protein) have also been used to manage SIADH. Unfortunately, there are no guidelines to follow, and such diets are generally contraindicated in patients with comorbidities such as heart failure and kidney disease. Demeclocycline has been used successfully to treat hyponatremia, but its effects are variable and it can be nephrotoxic.$^{20}$ Urea induces an osmotic diuresis and concomitant free water excretion. However, its use is very limited by an unpleasant bitter taste and the lack of availability in many countries.$^{20}$ Vasopressin receptor antagonists (also known as “vaptans”) have a US Food and Drug Administration (FDA) indication for “the treatment of clinically significant hypervolemic or euvoeamic hyponatremia (associated with heart failure, cirrhosis or SIADH) with either a serum $[Na^+]$ level <125 mEq/L or less marked hyponatremia that is symptomatic and resistant to fluid restriction.” The use of vaptans in patients with pneumonia has not been studied specifically or extensively (unlike patients with heart failure or cirrhosis), and therefore should be used with extra caution in this group, under the supervision of a nephrologist. Additional studies are needed to evaluate long-term clinical outcomes and cost/benefit ratios for the use of vaptans in patients with SIADH.

**SUMMARY**

The presence of hyponatremia in patients admitted with pneumonia should be recognized and actively managed. Isotonic fluids are generally appropriate initially to address underlying volume depletion and reduce the risk of hyponatremia developing during hospitalization. If hyponatremia persists once euvoeamic is achieved, patients are traditionally then managed with fluid restriction, increased dietary solute, or demeclocycline, each of which has significant limitations. Vasopressin receptor antagonists represent a new option for managing these patients, but must be used carefully under the supervision of a nephrologist.

**References**