In this case, the value for the TTKG of approximately 2 indicates that renal excretion of potassium is abnormally low for the prevailing hyperkalemia. Therefore, the inappropriately low TTKG indicates that the hyperkalemia is of renal tubular origin.

APPROACH TO MANAGEMENT

Knowledge of the factors controlling potassium secretion by the cortical collecting tubule principal cell can be helpful in understanding the basis for treatment of the hyperkalemia, especially if discontinuing the offending agent is not a reasonable clinical option. Potassium secretion is encouraged by a higher urine flow rate, increased distal delivery of sodium, distal delivery of a poorly reabsorbed anion (such as bicarbonate), and/or administration of a loop diuretic. Therefore, the approach to treatment in this patient should include intravenous 0.9% NaCl to expand the ECF and deliver more Na^+ and Cl^- to the cortical collecting tubule. In addition, because the trimethoprim molecule must be protonated to inhibit ENaC, alkalinization of the renal tubule fluid enhances distal tubular K^+ secretion. As an alternative to inducing bicarbonaturia to assist in potassium secretion, a carbonic anhydrase inhibitor may be administered to induce a kaliuresis. However, in the case presented here, for acetazolamide to be effective, the non-AG metabolic acidosis in this patient would first need to be corrected; Acetazolamide would, thus, require the coadministration of intravenous sodium bicarbonate for maximal benefit. Finally, systemic hyperkalemia directly suppresses renal ammoniagenesis, ammonium excretion, and, thus, acid excretion. Correcting the hyperkalemia with a potassium-binding resin (Kayexalate) is sometimes appropriate in these patients; the subsequent decline in the plasma K^+ concentration will also increase urinary ammonium excretion, helping correct the acidosis.

CASE 3

A 63-year-old man was admitted to the intensive care unit (ICU) with a severe aspiration pneumonia. Past medical history included schizophrenia, for which he required institutional care; treatment had included neuroleptics and intermittent lithium, the latter restarted 6 months before admission. The patient was treated with antibiotics and intubated for several days, with the development of polyuria (3–5 L/d), hypernatremia, and acute renal insufficiency; the peak plasma Na^+ concentration was 156 meq/L, and peak creatinine was 2.6 mg/dL. Urine osmolality was measured once and reported as 157 mOsm/kg, with a coincident plasma osmolality of 318 mOsm/kg. Lithium was stopped on admission to the ICU.

On physical examination, the patient was alert, extubated, and thirsty. Weight was 97.5 kg. Urine output for the previous 24 h had been 3.4 L, with an IV intake of 2 L/d of D_5W.

Laboratory Data					
Na 150	K 3.9	Cl 114	HCO_3^- 26	BUN 8	Creat 1.7
Glu 95	Alb 3.1	Ca 8.1	Phos 2.6	Mg 2.0	Plasma Osm 315
Urine:	Na 34	K 5.2	Osm 137		

After 3 days of intravenous hydration, a water deprivation test was performed. A single dose of 2 μg IV desmopressin (DDAVP) was given at 9 h (+9):

Laboratory Data					
Time (h)	0	+6	+8	+12	+18
Na^+	145	148	150	152	149
K^+	5.4	5.3	3.9	3.9	3.9
Cl^-	111	110	118	120	114
HCO_3^-	24	27	25	242	25
Creat	1.3	1.3	1.4	1.3	1.3
S_{osmol}	300	311	315		
U_{osmol}	132	140	201	237	257
AVP		8.4	6.3		

APPROACH TO DIAGNOSIS

Why did the patient develop hypernatremia, polyuria, and acute renal insufficiency? What does the water deprivation test demonstrate? What is the underlying pathophysiology of this patient's hypernatremic syndrome?

This patient became polyuric after admission to the ICU with severe pneumonia, developing significant hypernatremia and acute renal insufficiency. Polyuria can result from either an osmotic diuresis or a water diuresis. An osmotic diuresis can be caused by excessive excretion of Na^+-Cl^-, mannitol, glucose, and/or urea, with a daily solute excretion of >750–1000 mOsm/d (>15 mOsm/kg body water per day). In this case, however, the patient was excreting large volumes of very hypotonic urine, with a urine osmolality that was substantially lower than that of plasma; this, by definition, was a water diuresis, resulting in inappropriate excretion of free water and hypernatremia. The appropriate response to hypernatremia and a plasma osmolality >295 mOsm/kg is an increase in circulating vasopressin (AVP) and the excretion of low volumes (<500 mL/d) of maximally concentrated urine, i.e., urine with osmolality >800 mOsm/kg. This patient's response to hypernatremia was clearly inappropriate, due to either a loss of circulating AVP (central diabetes insipidus [CDI]) or renal resistance to AVP (nephrogenic diabetes insipidus [NDI]). Ongoing loss of free water was sufficiently severe in this patient that absolute hypovolemia ensued, despite the fact that approximately two-thirds of the excreted water was derived from the intracellular fluid compartment rather than the ECF compartment. Hypovolemia led to an acute decrease in the glomerular filtration rate (GFR), i.e., acute renal insufficiency, with gradual improvement following hydration (see below).

Following the correction of hypernatremia and acute renal insufficiency with appropriate hydration (see below), the patient was subjected to a water deprivation test followed by administration of DDAVP. This test helps determine whether an inappropriate water diuresis is caused by CDI or NDI. The patient was water restricted beginning in the early morning, with careful monitoring of vital signs and urine output; overnight water deprivation of patients with diabetes insipidus is unsafe and clinically inappropriate, given the potential for severe hypernatremia. The plasma Na^+ concentration, which is more accurate and more immediately available than plasma osmolality, was monitored hourly during water deprivation. A baseline AVP sample was drawn at the beginning of the test, with a second sample drawn once the plasma Na^+ reached 148–150 meq/L. At this point, a single 2-μg dose of the V_2 AVP receptor agonist DDAVP was administered. An alternative approach would have been to measure AVP and administer DDAVP when the patient was initially hypernatremic; however, it would have been less safe to administer DDAVP in the setting of renal impairment because clearance of DDAVP is renal dependent.

The patient's water deprivation test was consistent with NDI, with an AVP level within the normal range in the setting of hypernatremia (i.e., no evidence of CDI) and an inappropriately low urine osmolality that failed to increase by >50% or >150 mOsm/kg after both water deprivation and the administration of DDAVP. This defect would be considered compatible with complete NDI; patients with partial NDI can achieve urine osmolalities of 500–600 mOsm/kg after DDAVP treatment but will not maximally concentrate their urine to 800 mOsm/kg or higher.

NDI has a number of genetic and acquired causes, which all share interference with some aspect of the renal concentrating mechanism. For example, loss-of-function mutations in the V_2 AVP receptor cause X-linked NDI. This patient suffered from NDI due to lithium therapy, perhaps the most common cause of NDI in adult medicine. Lithium causes NDI via direct inhibition of renal glycogen synthase kinase-3 (GSK3), a kinase thought to be the pharmacologic target of lithium in psychiatric disease; renal GSK3 is required for the response of principal cells to AVP. Lithium also induces the expression of cyclooxygenase-2 (COX2) in the renal medulla; COX2-derived prostaglandins inhibit AVP-stimulated salt transport by the thick ascending limb and AVP-stimulated water transport by the collecting duct, thereby