for children. Bicarbonate is administered to adults with DKA for extreme acidemia (pH <7.1); for elderly patients (>70 years old), a threshold pH of 7.20 is recommended. Sodium bicarbonate, if administered, should only be given in small amounts. Because ketoacids are metabolized in response to insulin therapy, bicarbonate will be added to the ECF as ketoacids are converted. Overshoot alkalosis may occur from the combination of exogenously administered sodium bicarbonate plus metabolic production of bicarbonate.

5. *Phosphate.* In the first 6–8 h of therapy, it may be necessary to infuse potassium with phosphate because of the unmasking of phosphate depletion during combined insulin and glucose therapy. The latter drives phosphate into the cell. Therefore, in patients with DKA, the plasma phosphate level should be followed closely, but phosphate should never be replaced empirically. Phosphate should be administered to patients with a declining plasma phosphate once the phosphate level declines into the low-normal level. Therapy is advisable in the form of potassium phosphate at a rate of 6 mmol/h.
6. *Always seek underlying factors*, such as infection, myocardial infarction, pancreatitis, cessation of insulin therapy, or other events, responsible for initiating DKA. The case presented here is illustrative of this common scenario.
7. Volume overexpansion with IV fluid administration is not uncommon and contributes to the development of hyperchloremic acidosis during the later stages of treatment of DKA. *Volume overexpansion should be avoided.*

CASE 2

A 25-year-old man with a 6-year history of HIV-AIDS complicated recently by *Pneumocystis jiroveci* pneumonia (PCP) was treated with intravenous trimethoprim-sulfamethoxazole (20 mg trimethoprim/kg per day). On day 4 of treatment, the following laboratory data were obtained:

Laboratory Data	Units	Plasma	Urine
Na^+	meq/L	135	60
K^+	meq/L	6.5	15
Cl^-	meq/L	110	43
HCO_3^-	meq/L	15	0
pH		7.30	5.5
BUN	mg/dL	14	—
Creatinine	mg/dL	0.9	—
Osmolality	mOsm/kg H_2O	268	270

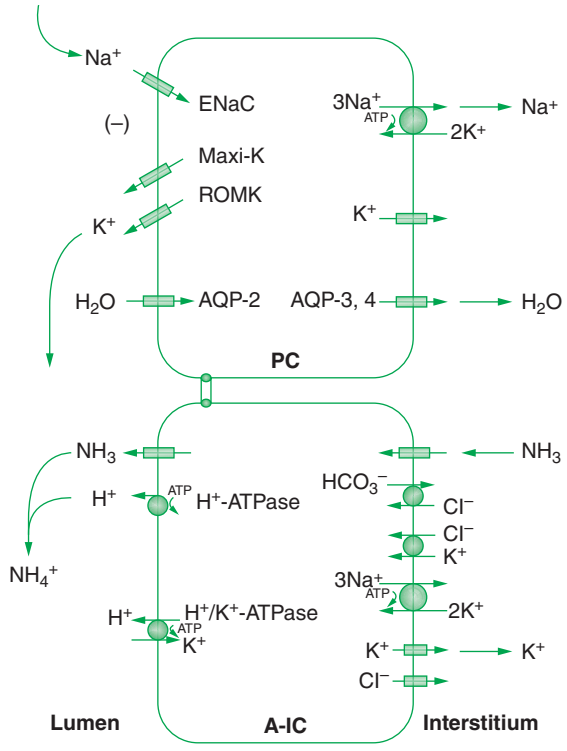

FIGURE 64e-1 Water, sodium, potassium, ammonia, and proton transport in principal cells (PC) and adjacent type A intercalated cells (A-IC). Water is absorbed down the osmotic gradient by principal cells, through the apical aquaporin-2 (AQP-2) and basolateral aquaporin-3 (AQP-3) and aquaporin-4 (AQP-4) channels. The absorption of Na^+ via the amiloride-sensitive epithelial sodium channel (ENaC) generates a lumen-negative potential difference, which drives K^+ excretion through the apical secretory K^+ channel, ROMK (renal outer medullary K^+ channel), and/or the flow-dependent maxi-K channel. Transepithelial ammonia (NH_3) transport and proton transport occur in adjacent type A intercalated cells, via apical and basolateral ammonia channels and apical H^+-ATPase pumps, respectively; NH_4^+ is ultimately excreted in the urine, in the defense of systemic pH. Electrogenic proton secretion by type A intercalated cells is also affected by the lumen-negative potential difference generated by the adjacent principal cells, such that reduction of this lumen-negative electrical gradient can reduce H^+ excretion. Type A intercalated cells also reabsorb filtered K^+ in potassium-deficient states, via apical H^+/K^+-ATPase.

APPROACH TO DIAGNOSIS

What caused the hyperkalemia and metabolic acidosis in this patient? What other medications may be associated with a similar presentation? How does one use the urine electrolyte data to determine if the hyperkalemia is of renal origin or due to a shift from the cell to the extracellular compartment?

Hyperkalemia occurs in 15–20% of hospitalized patients with HIV/AIDS. The usual causes are either adrenal insufficiency, the syndrome of hyporeninemic hypoaldosteronism, or one of several drugs, including trimethoprim, pentamidine, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, spironolactone, and eplerenone. Trimethoprim is usually given in combination with sulfamethoxazole or dapsone for PCP and, on average, increases the plasma K^+ concentration by about 1 meq/L; however, the hyperkalemia may be severe. Trimethoprim is structurally and chemically related to amiloride and triamterene and, in this way, may function as a potassium-sparing diuretic. This effect results in inhibition of the epithelial sodium channel (ENaC) in the principal cell of the collecting duct. By blocking the Na^+ channel, K^+ secretion is also inhibited; K^+ secretion is dependent on the lumen-negative potential difference generated by Na^+ entry through the ENaC (Fig. 64e-1).

Trimethoprim is associated with a non-AG acidosis that parallels development of hyperkalemia such that the co-occurrence of hyperkalemia and metabolic acidosis is not uncommon in this setting. H^+ secretion via apical H^+-ATPase pumps in adjacent type A intercalated cells (Fig. 64e-1) is also electrogenic, such that the reduction in the lumen-negative potential difference due to trimethoprim inhibits distal H^+ secretion; this is often referred to as a "voltage defect" form of dRTA. Systemic hyperkalemia also suppresses renal ammoniagenesis, ammonium excretion, and, thus, acid excretion; i.e., hyperkalemia per se has multiple effects on urinary acidification.

The inhibitory effect of trimethoprim on K^+ and H^+ secretion in the cortical collecting tubule follows a dose-response relationship, and therefore, the higher doses of this agent used in HIV/AIDS patients with PCP or in deep tissue infections with methicillin-resistant *Staphylococcus aureus* (MRSA) result in a higher prevalence of hyperkalemia and acidosis. Conventional does of trimethoprim can also induce hyperkalemia and/or acidosis in predisposed patients, in particular the elderly, patients with renal insufficiency, and/or those with baseline hyporeninemic hypoaldosteronism.

One means by which to assess the role of the kidney in the development of hyperkalemia is to calculate, from a spot urine and coincident plasma sample, the transtubular potassium gradient (TTKG). The TTKG is calculated as $(P_{osmol} \times U_{Potassium})/(P_{Potassium} \times U_{osmol})$. The expected values of the TTKG are <3 in the presence of hypokalemia (see also Case 7 and Case 8) and >7–8 in the presence of hyperkalemia.