**Educational Review Article**
http://journals.sbmu.ac.ir/jpn
https://doi.org/10.22037/jpn.v9i1.33191

# A Teenager Presents With Hypokalemia and Metabolic Alkalosis

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**Received:** November, 2020
**Accepted:** December, 2020

## Abstract

Hypokalemia is one of the most common electrolyte disorders in hospitalized patient. Causes of hypokalemia include impaired renal potassium ($K^+$) excretion, gastrointestinal losses or transcelluar shifts. Assessments of urinary $K^+$ excretion, acid-base status, and blood pressure are three major components to the causes of hypokalemia.
A random urine $K^+$-to-creatinine ($K^+$/Cr) less than 13 mEq/g Cr (<1.5 mEq/mmol) in a patient with hypokalemic metabolic alkalosis suggests poor intake, surreptitious vomiting, congenital pyloric stenosis, a shift of $K^+$ from extracellular fluid into the cells, laxative abuse, familial or sporadic periodic paralysis. In the setting of hypertension, urine K/Cr >1.5 mEq/mmol indicates primary and secondary hyperaldosteronism, Liddle syndrome, or apparent mineralocorticoid excess. By contrast, in the absence of hypertension, a urine $K^+$ /Cr>1.5, is usually suggestive of surreptitious use of diuretic, Bartter syndrome or Gitelman syndrome. Measurements of the plasma renin activity and plasma aldosterone concentration are necessary to differentiate these conditions from one another. Severe or symptomatic hypokalemia, if not recognized early or treated appropriately can lead to significant mortality and morbidity. In this article the basic principles of normal $K^+$ homeostasis and the pathophysiology that can disturb this balance are discussed. A selected case report focusing on the essential aspect of patient's presentation, signs and laboratory data followed by series of questions with particular attention to the diagnosis and management of hypokalemia needed to assist in the differential diagnosis and treatment are also discussed. Each question is followed by detailed discussion and reviews the recent publications that are useful at the bedside.
**Keywords:** Hypokalemia; Metaboloc alkalosis; Causes; Diagnoses; Treatment.

**Conflict of interest:**The author declared no conflict of interest.
**Please cite this article as**: Assadi F. A Teenager Presents With Hypokalemia and Metabolic Alkalosis: an Educational Review. J Ped Nephrol 2021;9(1):1-7.
https://doi.org/10.22037/jpn.v9i1.33191

## Introduction

Approximately 90% of the total body potassium ($K^+$) is located in the intracellular compartment, as a result of the $Na^+$-$K^+$-adenosine triphosphate (ATPase) activity on the cell membranes. The intracellular fluid (ICF) $K^+$ concentration is approximately 120-150 mEq/L, while extracellular fluid (ECF) $K^+$ concentration is maintained at about 4 about mEq/L.

The considerable concentration difference between intracellular and extracellular $K^+$ is essential to the maintenance of the membrane potential. $K^+$ distribution between ICF and ECF are achieved by matching $K^+$ intake with excretion and kidney is primarily responsible for maintaining $K^+$ homeostasis, with shifts of K+ between ICF and ECF compartments. For

example, in a 30 kg child subject the ECF volume is 6 liters. Therefore, the total amount of $K^+$ contained within the ECF space is 24 (6 x 4) mEq. A typical daily diet of 30 kg child may contain 50 mEq of $K^+$ (~2mEq/kg), 90% (45 mEq) of which initially enters the ECF compartment, raising the ECF $K^+$ concentration up to 11.5 mEq/L (24+ 45=69 ÷6 L). The marked increased in the plasma $K^+$ is faster than the kidneys to excrete it. Obviously, this does not occur, because this large quantity of $K^+$ fluxes into the ICF compartment by the increased activity of $Na^+$-$K^+$-ATPase of the cell membrane until the kidney excrete the 45 mEq $K^+$ load (3,4). This rapid cellular uptake of $K^+$ is stimulated by insulin and probably long-term by aldosterone. These hormones increase the activity of the $Na^+$- $K^+$-ATPase, particularly in muscle, liver, and adipose tissue. The principal stimulus for increased aldosterone release is a rise in plasma $K^+$. There is also evidence to suggest that insulin release is $K^+$ sensitive and has an effect on cellular $K^+$ uptake through absorption of glucose and amino acids from the gastrointestinal tract (6).

Clinically, a subject with an extracellular $K^+$ concentration of less than 3.5 mEq/L is referred to as hypokalemia, while a subject with an extracellular $K^+$ concentration of more than 5.5 mEq/L is referred to as hyperkalemia (1-3).

**Renal handling of potassium**

Under normal condition the daily load of $K^+$ is extremely low. The daily urine $K^+$ excretion in a normal subject (GFR 120 mL/min/1.73 $m^2$ or 180 L/day with serum $K^+$ 4.0 mEq/L) is about 720 mEq (4 mEq/Lx180 L/day=720 mEq/day). Approximately 65% of the filtered $K^+$ is reabsorbed in the proximal tubule. The thick ascending limb of the Henle loop reabsorbs an additional 25% of the filtered K+. The remaining 10% of the filtered $K^+$ load (72 mEq/day) reaches the distal nephron. However, the kidney excretes an amount of $K^+$ that is equivalent to approximately 20% of the filtered load (144 mEq/day). Since only 10% of the filtered load (72 mEq/day) is delivered to the distal nephron, $K^+$ secretion into the tubular lumen must occur at the level of collecting tubule. The rate of $K^+$ excretion is determined by rate of $K^+$ secretion by the principal cells of the collecting tubule (3,4).

When the total body $K^+$ is depleted, the tubular secretion of $K^+$ stops and the rate of $K^+$ excretion falls to 1% to 2% of the filtered load (7-14 mEq/day). In contrast, under conditions of $K^+$ excess, $K^+$ excretion may reach levels that are equal to or greater than the filtered load. Suppose that plasma $K^+$ concentration has increased to 6 mEq/L. Under this condition, the daily filtered load of $K^+$ would be 180 L/day x 6 mEq/L = 1080 mEq/day. Approximately 10% of the filtered load, or 108 mEq, is delivered to the distal nephron. However, the amount of $K^+$ excreted would be greater than the filtered load. Since 108 mEq $K^+$ is delivered to the distal nephron, this suggests that 972 mEq/day of $K^+$ (1080 mEq - 108 mEq) must be secreted by the distal and collecting tubules. Several factors can affect the rate of $K^+$ section including plasma $K^+$ concentration, tubular flow rate and a change in ECF pH, hypertonicity, cell lysis, exercise, and a fall in ECF pH (metabolic acidosis) can cause hyperkalemia as a result of enhanced flux of $K^+$ from ICF to ECF. In comparison, increased ECF pH (metabolic alkalosis) promotes an efflux of $H^+$ from the ICF. To maintain electrical balance across the membrane, there is a reciprocal flux of $K^+$ from the ECF to the ICF, thereby reducing ECF $K^+$ concentration (1-4).

The rate of $K^+$ secretion increases as ECF $K^+$ concentration increases. Increase in plasma $K^+$ directly stimulates aldosterone release which, in turn, increases $NA^+$- $K^+$-ATPase activity in the collecting tubule. Any reduction in absorptive capacity of proximal tubule and thick ascending tubule reduces $K^+$ reabsorption and more $K^+$ is delivered to the collecting tubule under this condition. The increased sodium entry into cell stimulate basolateral membrane $Na^+$- $K^+$-ATPase activity and therefore increases intracellular $K^+$ concentration and also increases lumen-negative potential thereby increasing the electrical gradient for $K^+$ efflux across this membrane (5).

**Hypokalemia**

Mild hypokalemia (>3.0 mEq/L) rarely causes symptoms and may be treated with oral $K^+$ supplements. Moderate to severe hypokalemia (< 3.0 mEq/L) generally produces muscle weakness and may lead to cardiac and respiratory failure and require intravenous $K^+$ supplementation (4,6).

Other symptoms may include nausea, vomiting, ileus, tetany and cardiac arrhythmias and ECG abnormalities (ST segment depression, short T wave with the appearance of U wave at the end of T wave (4-6).

Hypokalemia can result from poor intake, excessive loss from the body, or sudden shift of $K^+$ from ECF into cells. The most common causes are excess losses from the kidneys or gastrointestinal tract. Increased distal sodium delivery and urine flow rate are the most frequent causes of hypokalemia. Typically, this is often associated with mineralocorticoid excess, use of diuretics, or losses associated with increased urine flow, such as osmotic diuresis (7,8). Hypomagnesemia can also cause hypokalemia. Magnesium is required for adequate renal handling of $K^+$. This may become apparent when hypokalemia persists despite $K^+$ supplementation. A special case of $K^+$ loss occurs with diabetic ketoacidosis. In addition to urinary losses from polyuria and volume depletion, there is also obligate loss of $K^+$ from renal tubules as a cation partner to the negatively charged β-hydroxybutyrate. Familial hypokalemic periodic paralysis is a rare autosomal dominant disease characterized by transient episodes of profound hypokalemia due to a sudden transcellular shift of $K^+$ into cells. Episodes are typically precipitated by a large carbohydrate meal or strenuous exercise, but variants have been described without these features (7,8).

**Diagnostic approach**

Strategies to diagnose hypokalemia should be tailored to the underlying causes from history, physical examination and laboratory data. Potential processes, which can be identified in the history, include diet, vomiting, diarrhea and the use of laxatives, insulin, diuretics, or bicarbonate supplements and muscle weakness and polyuria (9,10).

Assessments of urinary $K^+$ excretion, acid-base status, and blood pressure are three major components to the causes of hypokalemia (7-10). Assessment of $K^+$ excretion is best accomplished by measuring $K^+$ in a 24-hour urine collection. Random measurement urine $K^+$/Cr is also an accurate and reliable method to assess renal K excretion (11-13). A random urine $K^+$ /Cr less than 13 mEq/g Cr (<1.5 mEq/mmol) in a patient with hypokalemic metabolic alkalosis is evidence of appropriate urinary $K^+$ excretion and suggests poor intake, surreptitious vomiting, congenital pyloric stenosis, or a shift of $K^+$ from extracellular fluid into the cells. Similar response can be seen in some patients with laxative abuse. If hypokalemia is associated with episodic muscle weakness, then consider hyperthyroidism, familial or sporadic periodic paralysis (11-13) (Figure 1). A urine $K^+$/Cr >1.5 mEq/mmol indicates inappropriate renal $K^+$ loss. In the setting of hypertension this is most often due to all causes of primary and secondary hyperaldosteronism, Liddle syndrome, or apparent mineralocorticoid excess (AME} (11-13). Measurements of the plasma renin activity (PRA) and plasma aldosterone concentration (PAC) are necessary to differentiate these conditions (Figure 1) (14).

In the setting of normal blood pressure a urine $K^+$ /Cr>1.5, is usually suggestive of surreptitious use of diuretic, Bartter syndrome or Gitelman syndrome (11-13). Measuring the urine sodium and chloride in addition to the urine $K^+$/Cr can help distinguish such conditions (Figure 2). If the urine sodium and chloride are approximately equivalent, Bartter or Gitelman syndrome is likely, whereas gastrointestinal wasting, laxative or diuretics use are likely if the urine sodium is substantially higher than the urine chloride excretion.

Primary aldosteronism should be suspected when PRA is suppressed and plasma PAC is increased. Secondary hyperaldosteronism (e.g., renal vascular hypertension, rennin-secreting tumor, and coarctation of the aorta) should be suspected when both plasma PRA and PAC are increased (15,16). Liddle syndrome is a rare hereditary disorder that is caused by a genetic abnormality that increases activity of the renal epithelial sodium channels (ENaC) on the luminal membrane in the collecting duct, which causes the kidneys to excrete $K^+$ in exchange for sodium leading to hypokalemia, hypertension, and metabolic alkalosis (17).

The syndrome of AME is an autosomal recessive form of hypertension in which 11-βhydroxysteroid dehydrogenase gene *(HSD11B2)* is defective (18). Under normal condition, this enzyme inactivates circulating cortisol to the less active metabolite cortisone.

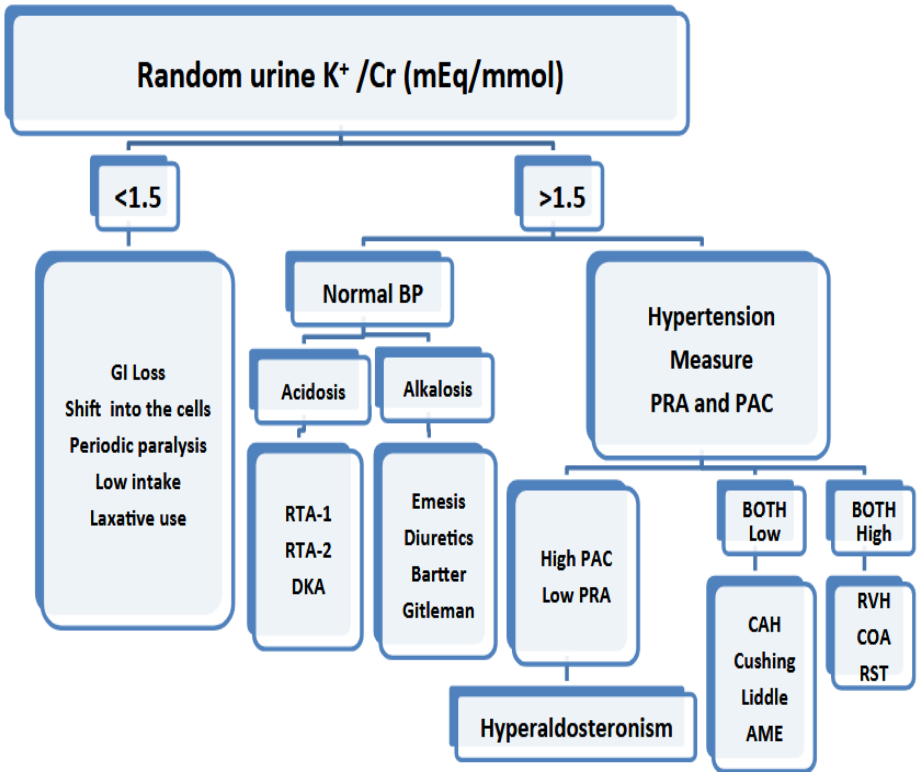


**Figure 1**. Diagnostic algorithm in hypokalemia. $K^+$/Cr; potassium-to-creatinine ratio, GI; gastrointestinal, BP; blood pressure, PRA; plasma renin activity, PAC; plasma aldosterone concentration, RTA; renal tubular acidosis, DKA; diabetic ketoacidosis, CAH; congenital adrenal hyperplasia, MAE; apparent mineralocorticoid excess, RVH; renal vascular hypertension, COA; coarctation of the aorta, RST, renin secreting tumor

In affected individuals, the increased level of cortisol can activate the mineralocorticoid receptors due to the non-selectivity of receptors leading to hypertension, hypokalemia, and hypernaremia. This can also occur in patients with congenital adrenal hyperplasia (17-α – hydroxylase deficiency) or familial cortisol resistance and in patients with severe Cushing syndrome. Chronic ingestion of natural licorice products, which contain glycyrrhetinic acid can mimic the clinical features of AME because it inhibits the 11-βhydroxysteroid dehydrogenase. Diagnosis of AME syndrome can be made by measuring the ratio of free urinary cortisol to free urinary cortisone. The ration is much higher in AME patients than non-affected patients (18).

Bartter syndrome is a rare hereditary disorder caused by a defect in the thick ascending loop of Henele and is characterized by hypokalemia, metabolic alkalosis, normal blood pressure, and hypercalciuria. Gitelman's syndrome is caused by loss of function mutations in a thiazide-sensitive ion transport mechanism in the distal nephron and is associated with hypokalemic metabolic alkalosis, and normal blood pressure. A patient with Gitleman syndrome, unlike patients with Bartter syndrome, their calcium excretion is normal (19).

**Treatment**

Intravenous $K^+$ must be given to patients with severe hypokalemia (serum $K^+$<2.5 to 3.0 mEq/L) or symptomatic (arrhythmias, marked muscle weakness) patients. Typically 0.9% saline is infused with 40 mEq KCl per liter at a rate of 10 mEq/hr over 3-4 hours. Giving intravenous $K^+$ at faster rate is not recommended as it may predispose to ventricular arrhythmia.

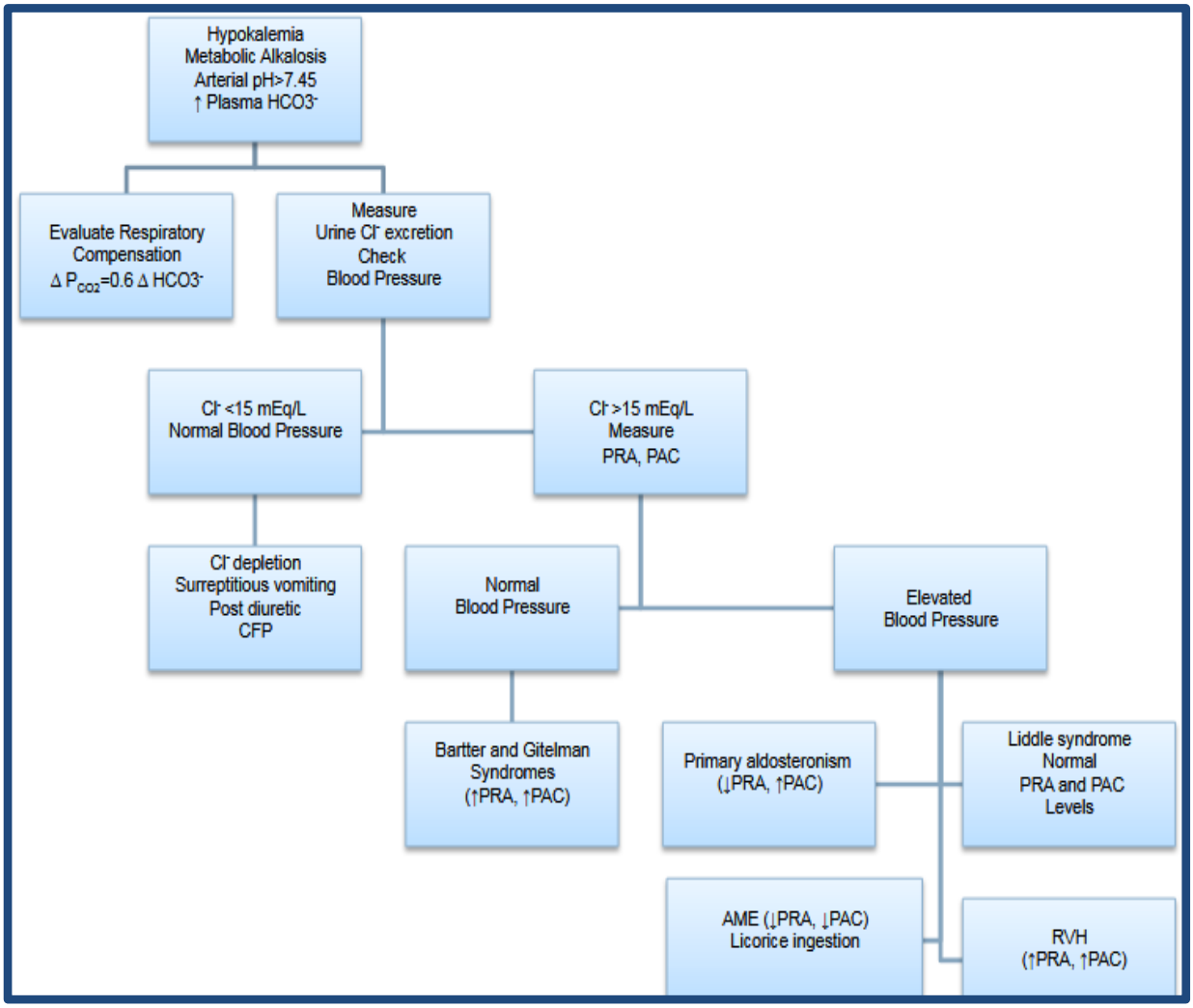


**Figure 2.** Diagnostic algorithm in metabolic alkalosis. $Cl^-$, chloride, $HCO3^-$; bicarbonate, PRA; plasma renin activity, PAC; plasma aldosterone concentration, CFP; cystic fibrosis of Pancreas, AME; apparent mineralocorticoid excess.

Glucose solutions are avoided because elevation in the plasma insulin levels could result in transient worsening of hypokalemia (20). When giving $K^+$ intravenously, infusion via central line is encouraged to avoid the rare occurrence of phlebitis. Hypokalemia due to the renal losses of $K^+$ may be amenable to a K-sparing diuretic such as amiloride or spironolactone, as these diuretics reduce the renal excretion of $K^+$. In a recent clinical trial, acetazolamide in combination with, standard therapy was found to significantly improve renal response to indomethacin, spironolactone, and enalapril in children with refractory Bartter syndrome (21).

## Case study

A 15-year-old girl was referred for evaluation of hypokalemia. She has no significant past medical history and denies the use of any medications.

She complains of muscle weakness and occasional abdominal pain.

Repeat laboratory data show hemoglobin 13 g/dL, BUN 16 mg/dL, serum creatinine 1.0 mg/dL, sodium 140 mEq/L, $K^+$ 2.4 mEq/L, chloride 101 mEq/L, $HCO3^-$ 32 mEq/L, calcium 9.0 mg/dL, magnesium 1.3 mg/dL, phosphorous 3.8 mg/dL and albumin 4.5 g/dL.

## Questions

**1. If we proceed in a step-wise fashion to make the diagnosis, which study would be the best initial laboratory study for the diagnosis of the altered electrolytes disorders?**

A. Urine diuretic screen
B. 24-hour urine for calcium, magnesium, and creatinine
C. Plasma renin and aldosterone levels
D. Arterial blood gases
E. 24-hour urine for sodium, $K^+$ and creatinine

The daily urinary magnesium excretion was 120 mg, calcium 485 mg, and creatinine 820 mg.

**2. Which diagnoses should receive further consideration (Select all that apply)?**

A. Primary aldosteronism
B. Bartter syndrome
C. Laxative abuse
D. Primary renal magnesium wasting
E. Loop diuretic abuse
F. Gitelman syndrome

**3. Which study would you like now to differentiate between Bartter syndrome and diuretic abuse?**

A. Urine diuretic screen
B. 24-hour urine for calcium, magnesium, and creatinine
C. 24-hour urine for sodium, $K^+$, and creatinine
D. Plasma renin and aldosterone levels

The urine diuretic screen was negative.
However, the laboratory calls to tell you that the urinary calcium excretion in the 24-hour collection was misreported-the correct value is 120 mg/24-hour NOT 485.

**4. What is the likely diagnosis now? (Select all that apply)**

A. Bartter syndrome
B. Gitelman syndrome
C. Primary aldosteronism
D. Primary renal magnesium wasting

**5. Which ONE of the following is the BEST answer?**

A. Hypokalemia can alter the renal handling of magnesium and cause hypomagnesemia
B. Hypomagnesemia can alter the renal handling of $K^+$ and cause hypokalemia
C. Both statements are true
D. Neither statement is true?

## Answers

**1. The correct answer is B.** Determination of the urinary magnesium excretion can help to differentiate gastrointestinal loss of magnesium from the renal magnesium wasting [1-4,9].

**2. The correct answers are B and E.** Hypokalemia, metabolic alkalosis, urinary calcium-creatinine ratio 0.59, renal magnesium wasting, and hypomagnesemia are clinical features of Bartter syndrome. Diuretic abuse is also a good choice because it causes the same type of transport defect (5-7).

**3. The correct answer is A**. A diuretic screen is the best way to differentiate between Bartter and chronic diuretic abuse.

**4. The correct answer is B**. Gitelman syndrome is the only one of these conditions which is associated with hypocalciuria. Gitelman syndrome is a variant of Bartter syndrome, characterized by hypokalemia, hypomagnesemia and hypovolemia (15).

**5. The correct answer is B.** Hypomagnesemia causes renal $K^+$ wasting likely by opening $K^+$ channels in the cortical thick ascending limb of the Henle loop. For this reason, the diagnosis of combined hypokalemia and hypomagnesemia is best approached by considering causes of hypomagnesemia (1-4, 9).

## Ethics

Written informed consent was obtained from patient for publication of this article

## Conflict of Interest

The authors declared no conflicts of interest.

## Financial Support

None to declare.

## Author Contributions

Farahnak Assadi contributed to data acquisition, analysis, interpretation, drafted the manuscript and approved the final manuscript as submitted.

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