



1-Minute Pearls/Pitfalls for the Clinician

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QUESTION 1: HOW SHOULD PHYSICIANS MANAGE HYPERKALEMIA IN PATIENTS ON BACTRIM FOR PJP PROPHYLAXIS?

A 48-year-old man with newly diagnosed HIV infection, currently receiving trimethoprim-sulfamethoxazole (Bactrim) for Pneumocystis jirovecii pneumonia (PJP) prophylaxis, is admitted for right lower extremity cellulitis. On admission, he is found to have hyperkalemia with a serum potassium level of 6.8 mEq/L, despite normal renal function. He denies the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or any medications other than his current HAART regimen. Electrocardiogram reveals peaked T waves, and he is appropriately treated with intravenous calcium gluconate, insulin with dextrose, and sodium zirconium cyclosilicate (Lokelma). He is started on a beta-lactam antibiotic for his cellulitis and shows a favorable clinical response. He reports a prior episode of asymptomatic hyperkalemia associated with Bactrim use over a year ago, also during treatment for cellulitis. His current CD4 count is 170 cells/ μ L. Given the recurrence of hyperkalemia likely related to Bactrim, what are the alternative options for PJP prophylaxis in this patient?

A: Regarding his HIV infection, PJP prophylaxis should be continued until his CD4 count has remained above 200/ μ L for more than three months in response to antiretroviral therapy. Alternatively, prophylaxis may be safely discontinued if his CD4 count remains between 100–200/ μ L and his HIV plasma RNA levels are undetectable for at least three months.¹

Bactrim-induced hyperkalemia is primarily due to the trimethoprim component, which acts on the distal tubule and collecting ducts. Trimethoprim functions as a competitive inhibitor of epithelial sodium channels in the distal nephron, similar to the potassium-sparing diuretic

Abstract

This article reviews pearls and pitfalls in managing hyperkalemia associated with Bactrim use for PJP prophylaxis, as well as strategies for addressing hypercalcemia induced by immune checkpoint inhibitors.

amiloride. This mechanism impairs potassium excretion, leading to hyperkalemia.^{2,3}

For patients who experience life-threatening allergic reactions or significant adverse effects from Bactrim, several alternative options for PJP prophylaxis are available¹:

- Dapsone: The use of this medication requires screening to ensure patients have no Glucose-6-Phosphate deficiency due to the risk for hemolysis in such patients with the use of Dapsone and other medications, which can cause oxidant damage in patients with this enzyme deficiency. The dose is 100mg daily.
- Atovaquone: The dose used is 1500 mg daily. Physicians should be aware of the risk of breakthrough PJP infections and dysgeusia.
- Aerosolized monthly pentamidine: This requires appropriate techniques to prevent breakthrough cases of apical PJP. In immunocompromised non-HIV patients as in patients who are post hematopoietic stem cell transplant, IV Pentamidine is another option but data about its use in patients with HIV infection is lacking and hence it is not recommended.

In this patient, Bactrim-induced hyperkalemia—likely due to a tubular effect despite normal renal function—may be managed with a loop diuretic to promote kaliuresis if other strategies are not feasible. If this approach is taken, close monitoring of renal function and electrolytes is essential.

Trimethoprim can also induce aldosterone resistance, leading to type IV renal tubular acidosis (RTA), characterized by hyperkalemia and a non-anion gap metabolic acidosis. In such cases, fludrocortisone, a synthetic mineralocorticoid receptor agonist, has been used successfully

to lower potassium by enhancing renal excretion of potassium and hydrogen ions. However, due to its sodium-retaining effects, fludrocortisone may cause adverse outcomes such as peripheral edema, hypertension, and congestive heart failure. To mitigate these, concurrent use of a loop diuretic is often necessary when fludrocortisone is used to treat medication-associated type IV RTA.^{4,5}

QUESTION 2: HOW SHOULD PHYSICIANS MANAGE PEMBROLIZUMAB RELATED HYPERCALCEMIA?

A 57-year-old woman with a recent diagnosis of stage 4 lung cancer, without evidence of bone metastases, has been receiving pembrolizumab every 3 weeks for the past 6 months. She is admitted with complaints of abdominal pain and constipation. Her latest PET scan showed a reduction in the size of her left lung mass and mediastinal/hilar lymphadenopathy. On physical examination, she had bilateral rhonchi with scattered crackles and mild epigastric tenderness. Laboratory findings include: albumin 2.8 g/dL, calcium 14.7 mg/dL, phosphorus 3.5 mg/dL, PTH 7 pg/mL (normal: 24–91 pg/mL), 25-hydroxy vitamin D 58.9 ng/mL (normal: 30–100 ng/mL), 1,25-dihydroxy vitamin D 145 pg/mL (normal: 20–79 pg/mL), and ALP 159 U/L. Serum and urine protein electrophoresis (SPEP and UPEP) were sent. She was treated with intravenous fluids, IV furosemide, zoledronic acid, and a dose of calcitonin. What is the most likely etiology of her hypercalcemia?

A: Hypercalcemia in malignancies is usually due to:

- a. a. Osteolytic bony metastases
- b. b. The release of PTH-related protein
- c. c. Calcitriol production by the malignancy

In rare cases, hypercalcemia can be caused by medications such as excessive vitamin A or D, thiazide diuretics, and lithium. In patients with end-stage renal disease (ESRD), the development of tertiary hyperparathyroidism can also lead to hypercalcemia. Non-PTH-mediated hypercalcemia that is not due to vitamin D toxicity but is associated with elevated levels of 1,25-dihydroxy vitamin D typically results from increased macrophage activity in granulomatous diseases, such as sarcoidosis, Crohn's disease, fungal granulomas, berylliosis, lymphomas, and, less commonly, tuberculosis.^{6,7}

In this patient, the elevated 1,25-dihydroxy vitamin D level is notable. Immune checkpoint inhibitors (ICIs), such as pembrolizumab, target PD-1/PD-L1 protein pathways, which normally function to suppress T-cell activity. By blocking this pathway, ICIs can cause abnormal

activation of macrophages—particularly those expressing PD-L1—which in turn can result in increased 1,25-dihydroxy vitamin D production and subsequent hypercalcemia. In the absence of any clinical or imaging evidence of granulomatous disease, her hypercalcemia is likely related to pembrolizumab therapy. Management in such cases involves corticosteroids, which help restore calcium balance through three main mechanisms: reversing PD-1/PD-L1 blockade, inhibiting 25(OH)D-1 α -hydroxylase (thereby reducing 1,25-dihydroxy vitamin D synthesis), and suppressing osteoclast-mediated bone resorption.⁸

For patients who cannot tolerate steroids, alternatives such as ketoconazole or hydroxychloroquine may be considered. There are case reports of immune checkpoint inhibitor-induced sarcoid-like reactions presenting with hypercalcemia and mediastinal or hilar lymphadenopathy. Therefore, in patients receiving immunotherapy, this adverse effect should be ruled out before assuming disease progression or the development of a new malignancy.⁸

Author contribution

All Authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the ICJME criteria of authorship.

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosures/Conflicts of Interest

The authors have no conflicts of interest to disclose.

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