

Prolonged Intravenous Colistin Use Associated with Acquired Bartter-Like Syndrome in an Adult Patient: A Case Report

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Abstract

Colistin-induced nephrotoxicity has widely been identified through the elevation of serum creatinine level or a reduction of glomerular filtration rate, but tubulopathy associated with colistin use is poorly understood. Herein, the authors describe a unique case of a 32-year-old quadriplegic male who developed persistent hypomagnesaemia, hypokalaemia, and metabolic alkalosis >4 weeks into therapy with intravenous colistimethate sodium for the treatment of decubitus sacral osteomyelitis by extensively drug-resistant *Klebsiella pneumoniae*. This required daily aggressive intravenous repletion of electrolytes and fluids while on the treatment, but it was only after 6 days of finishing the treatment with the antibiotic that metabolic changes resembling acquired Bartter-like syndrome started resolving.

INTRODUCTION

In recent years, intravenous (IV) colistin has become one of the few available agents to treat multidrug-resistant and extensively drug-resistant Gram-negative bacterial infections.^{1,2} Colistin exerts bactericidal activity against these agents by disrupting the bacterial cell membrane.³ Nephrotoxicity has been the most worrying side effect of the medication; as a result, the systemic use of colistin was discontinued in the 1970s, shortly after being introduced.² However, with limited alternatives and recent studies showing a relatively lower incidence of nephrotoxicity associated with

the use of more purified colistin (colistimethate instead of colistin sulphate), it has re-emerged as an important antimicrobial agent in a select group of patients.^{2,4} Most studies have demonstrated colistin-induced nephrotoxicity as acute kidney injury or acute tubular necrosis and have described it in the form of increasing creatinine, decreasing glomerular filtration rate (GFR), or the need to undergo haemodialysis.^{2,5-8} This paper, however, reports a unique case of acquired Bartter-like syndrome (BLS) after prolonged IV colistin therapy in an adult. Following a review of literature, only one case of BLS in an adult and one case in a preterm infant related to colistin use have been

reported.^{3,9} The exact pathophysiology for this type of tubulopathy associated with colistin use remains unclear.

CASE REPORT

A 32-year-old African-American male with a history of quadriplegia secondary to a gunshot wound to the neck, Stage IV ischial and sacral decubitus ulcers, and a history of recurrent wound infections secondary to soiling by faeces, presented initially to the hospital after being referred by an infectious disease specialist for evaluation for diverting colostomy placement. The patient's medical history was also significant for chronic respiratory failure and ventilator dependence status post tracheostomy, percutaneous gastrostomy tube dependence secondary to oropharyngeal dysphagia, dysfunctional bladder with chronic Foley catheter, sick sinus syndrome status post dual-chamber pacemaker placement, and recurrent multidrug resistant infections of the urinary tract and decubitus ulcers.

At the time of admission, the patient's blood pressure was 110/60 mmHg, heart rate was 60 beats per minute, and respiratory rate was 22 breaths per minute. The patient had a temperature of 37.9°C and was found to be less alert than normal. A physical examination also identified a 3.5x4.2 cm sacral ulcer with foul smelling drainage and a 1.6x2.3 cm right ischial ulcer. A probe-to-bone test was positive for sacral decubitus ulcer. The Foley catheter was replaced. Blood, urine, and wound cultures were sent for further testing. IV vancomycin and piperacillin-tazobactam were started. The patient underwent a successful diverting colostomy placement the next day. Blood cultures remained negative while urine culture grew a *Klebsiella pneumoniae* carbapenemase (KPC)-producing strain. Sacral wound culture was polymicrobial and grew KPC-producing strain, *Proteus mirabilis*, *Providencia stuartii*, and *Escherichia coli* on MacConkey agar. The presence of KPC was confirmed by Hodge Test and KPC was found to be resistant to imipenem with a minimum inhibitory concentration of 8 mg/L and sensitive to polymyxin B with dilution of 0.25 µg/mL.

Osteomyelitis could not be confirmed by MRI given the patient's history of pacemaker reliance and the patient was not able to tolerate nuclear bone scan. Since the patient's clinical picture was highly suggestive of decubitus sacral osteomyelitis, the infectious disease specialist decided to treat the patient with 6 weeks of IV antibiotics. Following the U.S. Centers for Disease Control and Prevention (CDC) recommendation, the patient was started on a 5 mg/kg daily dose of IV colistin, divided into 3 doses throughout the day, in combination with IV meropenem at 1 g every 8 hours for 6 weeks due to the synergistic action of colistin with carbapenem. A peripherally inserted central catheter was used for the administration of IV antibiotics. The patient's mental status improved, haemodynamics stabilised, and the patient was discharged back to a long-term acute care (LTAC) facility.

After 22 days, the patient was readmitted to the hospital from the LTAC facility for hypotension and fever. Initially, the patient's condition was suspected to be secondary to sepsis and, as a result, Gram-positive coverage with IV vancomycin was added to his ongoing regimen of IV colistin and meropenem. However, the cultures remained negative and the patient was noted to have recurrent early morning hypoglycaemia. Serum cortisol levels were 2.2 µg/dL, confirming adrenal insufficiency. The patient started IV stress dose hydrocortisone, which improved his overall clinical condition. IV vancomycin was discontinued, but the patient remained on IV colistin and IV meropenem. After 30 days on IV colistin, the patient started developing significant electrolyte disturbances. Laboratory analysis of serum constituent concentration revealed serum sodium 143 milliequivalents (mEq)/L, serum potassium 2.8 mEq/L, serum bicarbonate 29 mmol/L, serum magnesium 1.4 mg/dL, serum calcium 8.6 mg/dL, and serum creatinine of 0.25 mg/dL. On subsequent days, despite daily aggressive electrolytes repletion, the patient was noted to have persistent hypomagnesaemia, with levels as low as 1.1 mg/dL; persistent hypokalaemia, with levels between 2.5 and 3.4 mEq/L; metabolic alkalosis, with serum bicarbonate levels between 29 and 32 mEq/L; and polyuria, with urine output of around 4.0–4.5 L daily. Serum creatinine remained

within the normal range of 0.25–0.60 mg/dL. The patient did not have any diarrhoea or vomiting. Urine studies were carried out, and the patient's fraction excretion of magnesium was calculated to be 24%, confirming renal wasting. Urine potassium, urine calcium, and urine chloride concentrations were not obtained. The nephrology department followed the patient. In the absence of any other medications, including diuretics or aminoglycosides, unexplained electrolyte disturbances were most likely suggestive of tubulopathy associated with prolonged colistin therapy with resultant acquired BLS. However, due to the patient's complex medical history, the infectious disease specialist and nephrologist decided to complete the full 6-week course of IV colistin. The patient was kept in the hospital for close monitoring of his metabolic panel during therapy. The patient finished the 6-week course of IV colistin and IV meropenem and was discharged back to the LTAC facility on oral supplementation of magnesium and potassium for 3 days, along with close monitoring of blood work. Six days after the conclusion of therapy, repeat blood work at the LTAC facility started to show stabilisation of electrolytes levels.

DISCUSSION

Bartter syndrome is a hereditary, renal tubular salt-wasting disorder resulting from defective sodium chloride reabsorption in the medullary thick ascending limb of the loop of Henle and is characterised by hypokalaemia, metabolic alkalosis, hypochloreaemia, and hyperreninaemia with normal blood pressure.^{10–12} Based on the various genetic defects causing defective sodium chloride reabsorption, Bartter syndrome has been classified into type I, II, III, IV, IVb, and V.¹² Acquired BLS has also been described, especially following the use of aminoglycoside antibiotics.^{9,12,13} Certain diuretics and other medications, including amphotericin B, cyclosporine, and cisplatin, have also been associated with BLS.^{9,13} It is unclear how prolonged use of colistin can cause such tubulopathy.

In vitro electrophysiological studies have demonstrated that prolonged exposure to colistin can directly damage mammalian urothelium by interfering with transepithelial conduction.^{2,9,14} Also, similarly to aminoglycosides,

colistin may directly activate the calcium-sensing receptor in the medullary thick ascending loop of Henle, resulting in hypokalaemic metabolic alkalosis and hypomagnesaemia.^{2,9,13} This may also result in hypercalciuria and lower-than-normal serum calcium levels.^{2,9,13}

In the 5th week of IV colistin treatment, started on the 30th day of treatment, the patient started to develop persistent severe hypomagnesaemia, hypokalaemia, metabolic alkalosis, and polyuria, but serum calcium level, corrected for albumin, was normal. The patient was not taking any diuretics or other tuberculostatic medications. During readmission, the patient received IV vancomycin for 7 days from the 22nd to the 28th day of IV colistin therapy. However, the patient developed the aforementioned electrolyte disturbances 2 days after vancomycin was stopped. In addition, a review of the literature revealed that vancomycin-induced nephrotoxicity has been described as acute kidney injury resulting from acute interstitial nephritis or acute tubular necrosis.^{15,16} The authors were not able to find any data suggesting tubulopathy associated with vancomycin use in the absence of elevation of creatinine or reduction in GFR. Colistin has been associated with hypokalaemia,^{9,17} while other electrolyte disturbances are not well associated. In the patient, fraction excretion of magnesium was 24%, suggestive of urinary magnesium loss, along with polyuria with around 4.5 L of urine output daily. Urine potassium, calcium, and chloride were not analysed, which is a limitation of the case; however, there was no evidence of electrolyte loss from the gastrointestinal tract and no change in frequency or consistency of stools. Aggressive daily IV repletion of electrolytes and IV hydration were required to maintain metabolic balance. It was only after the cessation of IV colistin use after 6 weeks of treatment that the patient's metabolic panel started showing consistent improvement.

Colistin-induced nephrotoxicity is shown to be dose and duration dependent.^{2,7,18,19} As noted, the nephrotoxicity associated with colistin has mainly been reported as renal failure and deteriorating renal function in the form of an increase in serum creatinine, or decrease in GFR.^{2,5–8} Studies have also focussed on the need for renal replacement therapy.^{2,5–8} Tubular dysfunction or tubulopathy associated with

colistin use is not well described. In this case, the patient received colistin for 6 weeks, while in another two reported cases of colistin-associated acquired BLS, the adult patient received the treatment for 23 days and the preterm infant received the drug for 26 days.^{3,9} This may indicate that prolonged use of IV colistin, especially for >3 weeks, can result in tubulopathy. Patients may experience symptoms related to electrolyte disturbances, such as muscle cramps, fatigue, paraesthesia, or muscle spasms. Signs of volume depletion from polyuria may be present. Some patients may also develop ileus from hypokalaemia, and dyselectrolytaemia can predispose the patient to dysrhythmias. Therefore, the metabolic panel should be analysed periodically in those receiving IV colistin therapy for >2 weeks.

Reducing duration of treatment in certain infections can decrease the incidence of tubular dysfunction associated with colistin use.⁹ Additionally, the dosage of colistin administration should be adjusted for tubulopathies beside serum creatinine level and/or GFR.⁹ Finally,

the decision to stop colistin treatment based on renal dysfunction must be weighed against the consequences of withholding a potentially life-saving antibiotic.^{2,9} In this case, due to the patient's complicated and advanced medical problems, the infectious disease specialist decided to finish the course of antibiotics for 6 weeks despite the tubulopathy that developed in the 5th week of therapy.

CONCLUSION

Renal tubular dysfunction associated with IV colistin use should be kept in mind, especially while administering the antibiotic for a prolonged period. More pharmacological studies are needed to determine the optimal dosing regimen with colistin use to achieve adequate antibacterial activity while minimising associated toxicities.^{3,9} Finally, mild and reversible side effects developing with the medication administration should not preclude the patients from receiving the treatment for the course, as it may be the best option available against certain life-threatening infections.

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