A series of clinical cases highlighting cardiotoxicity induced by polymyxin B

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Abstract

Polymyxins, particularly polymyxin B, have resurfaced as critical agents against Multidrug-Resistant Organisms (MDROs) despite their historical withdrawal from clinical use due to significant nephrotoxicity and neurotoxicity. This resurgence is largely driven by the increasing prevalence of infections caused by Carbapenem-Resistant Enterobacterales (CRE) and Carbapenem-Resistant *Acinetobacter Baumannii* (CRAB). In this report, three clinical cases highlighting the association between polymyxin B administration and severe cardiac events, including ventricular tachycardia and cardiac arrest in patients with multiple co morbidities. The cardio toxic effects of polymyxins are attributed to their impact on cardiac myocyte ionic channels, particularly potassium channels, leading to arrhythmias and potential cardiovascular collapse. Given the rising use of polymyxins amidst escalating resistance patterns, it is imperative for clinicians to recognize and monitor for cardio toxicity, ensuring prompt intervention to mitigate risks associated with this potent antibiotic.

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Key words: polymyxin B, ventricular tachycardia, chronic kidney disease, ischemic heart disease, diabetes mellitus, hypertension.

Funding: this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest: the authors declare no conflict of interest.

Patient consent: the authors certify that they obtained the appropriate patient consent form. In the form, the patient(s)/relative have granted their consent for clinical information to be reported in the journal.

Ethics approval: not applicable.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Received: 9 December 2024.
Accepted: 31 March 2025.
Early view: 29 April 2025.

Licensee PAGEPress, Italy
Emergency Care Journal 2025; 21:13468
doi:10.4081/ecj.2025.13468

Introduction

Polymyxins, a class of antibiotics, were first introduced to clinical practice in 1947. However, they did not undergo the rigorous testing associated with contemporary medication approval procedures. Initially, these antibiotics were removed from therapeutic use due to significant neurological and renal impairments, along with the introduction of newer antibiotics. In the past decade, there has been resurgence in the use of polymyxins to treat infections caused by Multidrug-Resistant Organisms (MDRO), particularly Carbapenem-Resistant Enterobacterales (CRE) and Carbapenem-Resistant Acinetobacter Baumannii (CRAB), which are becoming increasingly prevalent worldwide. Over a 20-year period, the use of polymyxins decreased, leading to a reduction in nephrotoxicity; however, rates of neurotoxicity during this renewed usage have not been adequately documented.[1-4] This report examines patients who suffered from gram-negative septicemia and other co morbid conditions, ultimately dying of cardiac collapse after receiving a polymyxin B infusion.

Case Reports

Case 1

A 56-year-old male presented with fever, nausea, and generalized weakness, with a known history of hypertension, diabetes mellitus, ischemic heart disease, and Chronic Kidney Disease (CKD) post-renal transplant. He was admitted with generalized weakness and nausea persisting for seven days. A CT scan of the head was performed, revealing normal results. An upper GI endoscopy suggested candidial esophagitis, no other evidence of fresh or alter blood, gastric body and fundus normal, and duodenum normal, while a CT of the abdomen indicated a subcapsular collection. The patient was initially managed in the ward with imipenem-cilastatin injections and teicoplanin injections, but was later transferred to the ICU due to hypoxia and hypotension following an excisional lymph node biopsy. In view of worsening sepsis after sending cultures started with injections of polymyxin

B loading dose of 1,500,000 units loading followed by 750,000 units 12 hourly. After the second dose of polymyxin B, the patient developed ventricular tachycardia, leading to cardiac arrest (Figure 1). Investigation in the form of calcium, magnesium, potassium and phosphorus were also evaluated and were found to be in normal range. Despite resuscitative measures in accordance with recent AHA guidelines, the patient could not be revived.

Case 2

A 69-year-old male presented with pain in the scapular region and had a known history of ischemic heart disease, diabetes mellitus, and CKD requiring maintenance hemodialysis. He was taken for coronary artery angiography due to a positive troponin I test. A Percutaneous Transluminal Coronary Angioplasty (PTCA) with Drug-Eluting Stent (DES) and Intravascular Lithotripsy (IVL) was performed. An Intra-Aortic Balloon Pump (IABP) was inserted due to hypotension. Following the procedure, Sustained Low-Efficiency Dialysis (SLED) was initiated, which was later changed to Continuous Renal Replacement Therapy (CRRT) due to persistent hemodynamic instability. Infection workup revealed elevated CRP levels and intermittent fever spikes, prompting the initiation of antibiotics after blood and urine cultures were sent. Over time, the patient stabilized for few days with Meropenem injections and Teicoplanin injections, latter on patient again started having fever, hypotension and elevated infection markers; so after sending cultures, polymyxin B injection was started with a loading dose of 1,500,000 units followed by 750,000 units every 12 hours, he developed breathlessness and arrhythmias, specifically ventricular tachycardia. Electrolytes in the form of calcium, magnesium, potassium and phosphorus were also evaluated and were found to be in normal range. Despite CPR as per AHA guidelines, the patient could not be revived.

Case 3

A 67-year-old male presented with severe breathlessness and weakness for 7-10 days. Angiography indicated triple vessel disease, prompting a planned Coronary Artery Bypass Grafting (CABG). He had a known history of hypertension, diabetes mellitus, and CKD. Postoperatively, the patient's ICU stay was uneventful; however, he later exhibited drowsiness and was transferred back to the ICU. Blood and tracheal cultures revealed multidrug-resistant *Acinetobacter baumannii* and CRE *Klebsiella pneumoniae*, respectively and both were sensitive to colistin and polymyxin B only. So, polymyxin B was initiated, and after the first dose of 1,500,000 units, the patient developed atrial fibrillation with sustained ventricular tachycardia. Evaluation in the form of calcium, magnesium, potassium and phosphorus were also evaluated and were found to be in normal range. Following the second dose of 750,000 units, he experienced severe bradycardia, hypotension, and breathlessness. The patient was intubated, resuscitated, and required noradrenaline infusion. Polymyxin was discontinued, and treatment was adjusted according to culture sensitivity. The patient stabilized with Direct Current (DC) cardioversion and injection amiodarone. Later patient discharged with follow-up.

Discussion

Cardio toxicity associated with polymyxin B administration is a very rarely documented adverse effect.[1] The underlying mechanisms are multifactorial, primarily involving direct effects on cardiac myocytes. Polymyxins, including polymyxin B, disrupt ionic channels, particularly potassium channels, in cardiac cells, leading to action potential prolongation, QT interval prolongation, and various cardiac arrhythmias, including ventricular tachycardia and fibrillation.[2,3] The disruption of potassium channels is a key factor in the cardio toxic effects of polymyxins. Approximately 26%-

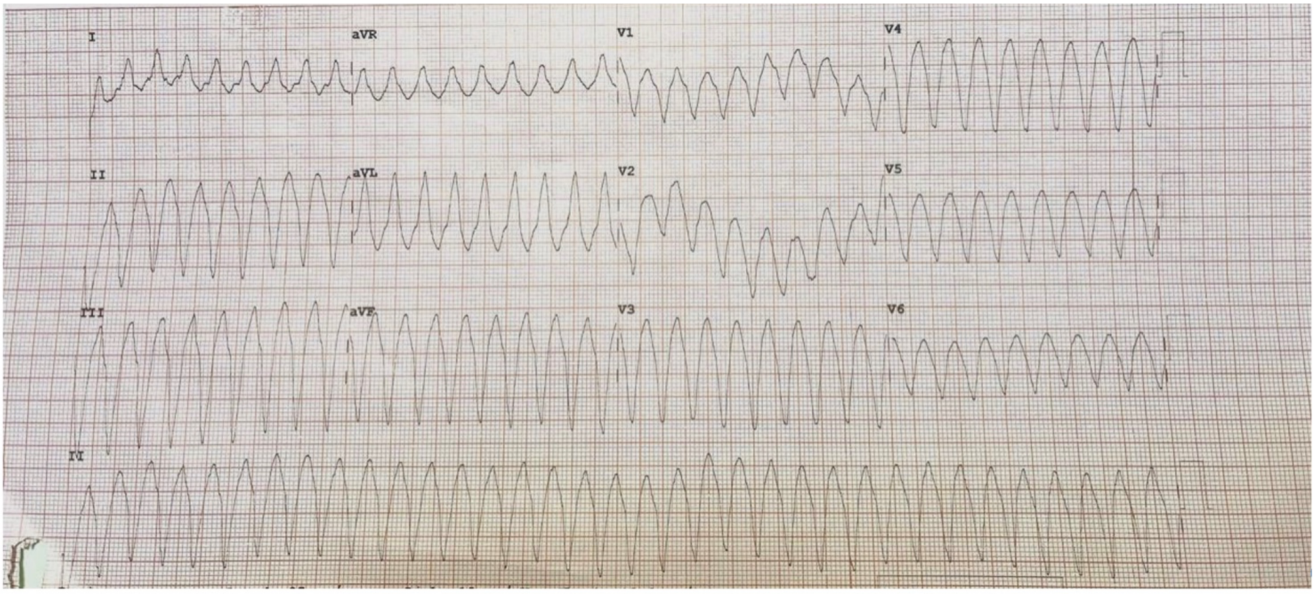

Figure 1. Ventricular Tachycardia ECG.

45% of the patients experience nephrotoxicity receiving injections polymyxin B.[4] Additionally, polymyxin B has been shown to induce oxidative stress and mitochondrial dysfunction in cardiac cells,[5] resulting in impaired cardiac contractility, reduced cardiac output, and potential cardiovascular collapse. A systematic review by Falagas and Kasiakou highlighted the significant risk of toxicity with polymyxin B use.[6] Risk factors for polymyxin B-induced cardiotoxicity include high doses, prolonged treatment duration, pre-existing cardiovascular co-morbidities, hypoxia, hypotension, impaired kidney function; concomitant use of neuro-blocking agents may contribute to toxicity related to polymyxin B infusion.[6,7] Among the potential mechanism of toxicity, it should be reminded that polymyxin B may cause also a non-competitive neuromuscular blockade (not responsive to cholinesterase inhibitor) that may lead to respiratory arrest and consequent cardiac arrest. There may be the possibility of polymyxin may cause respiratory distress especially in case 2, as discussed by Wunsch H and Lindesmith in their articles, but primarily ventricular tachycardia triggered the catastrophic event.[8,9] Clinicians must remain vigilant for signs of cardiotoxicity, such as arrhythmias, QT prolongation, and hemodynamic instability during polymyxin B therapy. Appropriate monitoring, dose adjustment, and close cardiovascular surveillance are essential to mitigate these risks.[10-12] In conclusion, the cardio toxic effects of polymyxin B are well-recognized and can be life-threatening. Understanding the underlying mechanisms and risk factors is crucial for the safe and effective use of this antimicrobial agent.

Conclusions

The reintroduction of polymyxins into clinical practice underscores the urgent need to address multidrug-resistant infections while recognizing the associated risks, particularly cardio toxicity. Our case reports illustrate that polymyxin B can precipitate serious cardiac complications, including ventricular tachycardia and bradycardia, especially in patients with pre-existing cardiovascular conditions. The mechanisms behind these adverse effects involve disruption of ionic channels and oxidative stress in cardiac cells. Clinicians must maintain a high index of suspicion for cardio toxicity during polymyxin therapy, employing vigilant monitoring and appropriate dosing strategies. As resistance to conventional antibiotics continues to rise, understanding the balance between efficacy and toxicity of polymyxins is crucial for optimizing patient outcomes. Future research should focus on refining dosing regimens and exploring adjunct therapies to enhance the safety profile of polymyxin B while preserving its therapeutic potential against resistant pathogens.

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