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Case Report

# Colistin Therapy-induced Acute Kidney Injury: A Case Report

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**ABSTRACT**

Nephrotoxicity refers to the RIFLE (R-risk, I-injury, F-failure, L-loss of function, E-end stage renal failure) categories. It is genetically acquired, caused by drugs, and also related secondarily to diabetes, liver problems, and cardiac problems. Drug-induced nephrotoxicity is dose-dependent. Colistin drug usage is uttermost in usage due to Multi-Drug Resistant (MDR) infections caused by gram-negative bacteria like *Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Acinetobacter baumannii*. We are reporting a case of a 62-year-old male patient suffered from Venous thromboembolism and Anemia who underwent fasciotomy later suffered with Hospital Acquired Pneumonia (HAP) caused by MDR *Acinetobacter baumannii* sensitive to only colistin and meropenem. Two days after the initiation of therapy, urine output was decreased (Oliguria-<500 mL), creatinine levels were increased to 3.08mg/dL and renal parenchymal changes were observed in USG. His laboratory reports suggest he developed Acute Kidney Injury (AKI) Colistin shows a probable (Naranjo score-8) causal relationship with AKI. The dose of the drug was not altered or stopped. Creatinine and BUN levels were closely monitored. After 14 days, urine output was increased to 2400mL. Other neurological side effects of Colistin such as respiratory failure was not observed. On the day of discharge, the patient was stable and improved. This means that if the benefit outweighs the risk, there is no need to discontinue the drug; close monitoring will reduce side effects.

**Keywords:** *Acinetobacter boumannii*, Oliguria, MDR, Nephrotoxicity, RIFLE.

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## INTRODUCTION

Colistin is a polymyxin antibiotic obtained from species *Bacillus polymyxa* from the species Bacillus in 1940's. It is the only drug in polymyxin category used clinically in 1960's but was withdrawn within a decade due to toxic side effects.[1] Later it came into use in 1990's for the treatment of MDR micro-organisms Gram-negative infections which include *Pseudomonas aeruginosa*, *Klebsiella pneumonia* and *Acinetobacter baumannii*.[1-7] Nephrotoxicity and respiratory failure are the ADR'S associated with Colistin. Occurrence of nephrotoxicity is more frequent when compared to neurological side effects. ADR occurrence was reduced with the use of purified form of Colistin-Colistimethate Sodium ranging from 0-37%.[2] Occurrence of side effect is dose dependent to the post antibiotic effect. Pathophysiology of nephrotoxicity is exactly not known but is demonstrated as increased membrane permeability, oxidative injuries, and subsequently acute tubular necrosis.[4-7] Apoptosis (via mitochondrial death receptor, and endoplasmic reticulum pathways), cell cycle arrest, autophagy, altered nitric oxide balance, mitochondrial dysfunction and oxidative stress.[2,4]

Risk factors for colistin nephrotoxicity include dose and duration of colistin therapy, coadministration of other nephrotoxic drugs, patient related factors such as age, sex, hypoalbuminemia, hyperbilirubinemia, underlying disease and severity of patient illness.[5] Other drugs that can cause nephrotoxicity are Analgesics, Antidepressants, Antibiotics (Aminoglysosides, Ganciclovir, Acyclovir, Amphoterisin B, Foscarnet sodium, Penicillins, Vancomycin, and Meropenems), Benzodiazepines, Antiretrovirals, Contrast media, and Diuretics.[2,7,8] Nephrotoxicity is measured in RIFLE (R- risk, I- injury, F- failure, L- loss, E- end-stage renal failure) categories.[7]

## CASE DESCRIPTION

A male patient aged 62 years was admitted in the emergency department with complaints of Swelling, pain and loss of sensation in the right lower limb for 2 days. On examination, patient had cold and discolored right lower limb. He was a known case of CVA and Hypertension and was treated with Cilnidipine 20mg, Telmisartan 40mg, and Prazosin 5mg BD, Clonidine 0.5mg. The patient had total knee replacement surgery two days back, there by admitted with the symptoms of acute compartment compression disease (right leg swelling, pain, loss of sensation) and

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underwent Fasciotomy. Post to the emergency procedure, patient suffered cardiac arrest and was given ventricular fibrillation shock. On performing CT angiogram, he was diagnosed with Venous thromboembolism in the right lower limb. Inferior Venacava (IVC) filter was placed and the right lower limb up to the above knee was amputated. Anticoagulant medication of low molecular weight heparin Apixaban 5 mg, Cefoperazone sulbactam 1 gm BID, Minocycline 100 mg BID, pantoprazole 40mg OD was given prophylactically. After 3 days of ICU stay patient diagnosed with Hospital acquired pneumonia based on clinical symptoms (SOB, fever with chills) and chest X-ray. Nebulization was given with duolin 12$^{th}$ hourly and budecort 8$^{th}$ hourly, following the same protocol as the first and second days, but the antibiotics were replaced with Inj. meropenem.

A multi-drug resistant gram-negative bacteria Acinetobacter was isolated from the sputum culture, which showed sensitivity to only colistin and meropenem antibiotics. To the above treatment regimen Colistin 3 IU BID is added on Day 5. After 48 hr of Colistin therapy, patient had decreased urine output (Oliguria-500 mL/day), his BUN levels were 92.3 mg/dL, and creatinine levels were 3.08 mg/dL, and renal parenchymal changes was observed in Ultra Sonography (USG) abdomen indicating acute kidney injury. The dose of the drug was not altered. Creatinine and BUN levels were closely monitored. On Day 13 Regimen was added with aspirin 75mg and atorvastatin 40mg as to prevent clotting of blood and remaining therapy is continued. After 1-week (day 14) RFTs were repeated and BUN (90mg/dL) and serum creatinine (2.4 mg/dL) levels were slightly decreased and Urine output was 900 mL/day. The patient had anemia with 7gm/dL of Hb and was undergone multiple blood transfusions, erythropoietin 4000 IU thrice a week, iron folic acid tablets, vitamin therapy, and chymoral forte added to the regimen. On Day 16, urine output increased to 2400 mL/day, creatinine and BUN levels decreased to 1.9 mg/dL and 47 mg/dL respectively and the patient was dischrged. Fate of creatinine and urine output during hospitalization was depicted in Figure 1. After 10 days Patient came for follow up RFT shows creatinine levels below 1mg/dl and BUN levels 18 mg/dL.

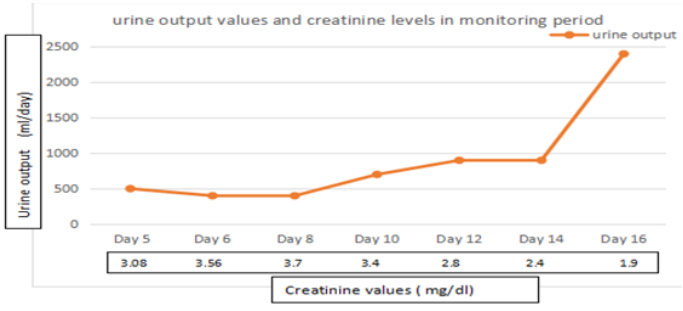


**Figure 1:** Indicates changes in creatinine and urine ouput after initiation of colistin therapy.

## DISCUSSION

Even though colistin use is appreciated in gram negative MDR infections it is a reserve drug. It causes life threatening nephrotoxicity and neurotoxicity. Some neurotoxic symptoms: dizziness, weakness, facial and peripheral paresthesia, vertigo, visual disturbances, confusion, ataxia, and neuromuscular blockade. Koch-Weser *et al.* reported the incidence of the neurotoxic manifestations to be about 7%, with paresthesia being the most common In this case, the patient developed nephrotoxicity 48 hr after the initiation of colistin; as said by the studies, nephrotoxicity was observed within 24 to 72 hr after initiation.[8] Nephrotoxicity development is collectively caused by age, other nephrotoxic drugs used concurrently, and the dose of colistin.[7] But according to Aydogan BB *et al.*, age is not a risk factor for colistin nephrotoxicity development.[3] The total amount of colistin use for pulmonary infection, and concomitant use of amphotericin and vasopressor were found to be risk factors in all study participants.[3] In this case patient was not given with loading dose. For every 12 hr given with 3M IU (240mg) of colistin, in his total length of stay in hospital given with 84MIU (20,160mg). Ayse Serra-Ozel *et al.* say that nephrotoxicity development is most likely (52.5%) in people who used both loading and maintenance doses, but further studies are needed in this segment.[6] The mean ± SD of cumulative dose in patients without nephrotoxicity was higher than that in those with nephrotoxicity, although this difference was not statistically significant.[9]

In this case, the patient was also treated with meropenem, prazosin, and aspirin more feasible for the development of nephrotoxic Colistin develops less nephrotoxicity (36.2%) when compared to beta-lactams (140%).[7,10] As per Dalal A. Al-Abdulkarim *et al.*, and spapen H *et al.* None of the patients required Renal Replacement Therapy, and AKI needed to recover within 13.8±23.8 days.[7,11] Here in this case patient recovered from AKI in about 14 days. Complete recovery from renal toxicity is observed in 21 days after initiation of therapy.

### Causality assessment

Relationship between colistin and nephrotoxicity is tested by using WHO and Naranjo's scales approved by Uppasala monitoring Centre. It indicates a probability of development with a score of 8. Dechallenge was not performed based on the benefit risk ratio. Treatment with colistin is mandatory, so renal function is monitored throughout the therapy. Life threatening renal and neurotoxic symptoms were not observed during the therapy period. Thus, dechallenging was not performed.

## CONCLUSION

There is a need for the stoppage of therapy even though, on occurrence of ADR. Colistin therapy initiation should be based on the benefit-risk ratio. If colistin therapy is highly recommended then based on the appearance of nephrotoxicity,

careful monitoring of kidney functions promotes recovery. No need of dechallenging of drug. Clinical pharmacist activities play a major role in dose alterations in severe ADRs.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**HAP:** Hospital Acquired Pneumonia; **MDR:** Multi Drug Resistant; **ADR's:** Adverse Drug Reactions; **CVA:** Cerebro Vascular Accident; **BD:** Twice in a day; **OD:** Once in a day; **TID:** Three times in a day; **CT:** Computed Tomography; **IVC:** Inferior Vena Cava; **ICU:** Intensive Care Unit; **SOB:** Shortness Of Breath; **EDTA:** Ethylene Diamine Tetracetate; **RFT:** Renal Function Test; **BUN:** Blood Urea Nitrogen; **MIU:** Million International Units; **IU:** International Units; **Hb:** Hemoglobin; **SD:** Standard Deviation; **AKI:** Acute Kidney Injury; **WHO:** World Health Organisation; **RIFLE:** Risk, Injury, Failure, Loss, End stage organ; **mg:** Milligram; **mL:** Millilitres; **USG:** Ultrasonography.

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