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CASE REPORT

Rifampin-like Red-brown Bronchial Secretions Staining in a Patient Treated with Cefiderocol

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SUMMARY

Numerous drugs are known to alter the colour of human body fluids. Although drug-induced bronchial secretions staining is normally harmless, it may frighten the patient and could lead to unnecessary clinical inquiries. Cefiderocol is often removed renally as an unmodified drug; bronchial secretion staining has not been seen at doses used in clinical practice. We report a possible first case of bronchoalveolar lavage staining occurred during Cefiderocol treatment in a critical patient.

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INTRODUCTION

Cefiderocol is a new siderophore cephalosporin antibiotic that binds ferric iron (Fe3+) and uses bacterial iron transporters for intracellular access (Principe L *et al.*, 2022; De Benedetto I *et al.*, 2022). Recently, several reports have described red-brown urine staining during cefiderocol treatment, especially at standard doses (i.e., 2g every 8 hours) (Smith M, Foong KS, 2023; Shapiro K, Ungar S, 2023; Lupia T, *et al.*, 2023). Commonly used antibiotics in clinical practice rarely stain human secretions. Nevertheless, rifampicin is reported to change the colour of body fluids, including airway secretions, to red-orange (Grosset J, Leventis S, 1983; Boeree MJ *et al.*, 2017) due to the degradation of naphthoquinone chromophore in the molecular structure of rifamycins and was more frequently reported at high dosages of rifampicin (Grosset J, Leventis S, 1983; Boeree MJ *et al.*, 2017).
Although drug-induced body fluid staining is normally harmless, it may frighten the patient and could lead to unnecessary clinical inquiries.

Key words:
Cefiderocol, fluid staining, bronchoalveolar lavage, TDM.

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CASE REPORT

Here we describe the first case, to our knowledge, of red-brown discoloration of bronchial fluids due to cefiderocol administration in a heart-transplanted patient. A 56-year-old man underwent heart transplantation due to a history of hypertrophic cardiomyopathy with an evolving hypocontractile-restrictive pattern. Fifteen days after transplantation, the patient presented septic shock, likely of pulmonary origin, with ventilator-associated pneumonia (VAP) and the growth of *Klebsiella pneumonia* carbapenemase-producing (KPC) in bronchoalveolar lavage and blood cultures. The patient was treated with meropenem/vaborbactamat standard dosage and 24g/die intravenous (IV) fosfomycin starting on the fifth postoperative day. After initiating the antibiotic therapy and facing worsened cardiac function and initial multi-organ failure, initial organ rejection was suspected. In the following week, the patient developed acute kidney injury (AKI) requiring continuous veno-venous hemofiltration (CVVH), and a sub-tamponade pericardial effusion. Due to persistent fever, an unsatisfactory respiratory response, and after evaluating local multidrug-resistant organisms epidemiology, antibiotic therapy was empirically modified to include cefiderocol2 g IV every 8 hours and daptomycin 700 mg IV. Within 72 hours, inflammatory markers decreased, and there was a slight improvement in respiratory status. However, on the sixth day of cefiderocol therapy a red-brown bronchoalveolar lavage (BAL) was reported (*Figure 1*).

The sample was tested to exclude alveolar haemorrhage, but no red blood cells or haemoglobin were observed (*Table 1*).

Therapeutic drug monitoring (TDM) of cefiderocol on a serum sample revealed a concentration of 81.8 mg/L and a bronchial secretion of 71.4 mg/L was detected. Blood and bronchial samples were collected two hours after cefiderocol administration at a dosage of 2g/q8h. CVVH was conducted with a heparinized circuit with the following settings: subtractive flow – 150 mL/h, BI – 400 cc, effluent flow rate 24 h, 2300 mL, on the day of pharmacokinetic sampling. Bronchial samples and plasma (after centrifugation of whole blood at 1600 g for 20 min) were collected in two cryovials for the analysis. Cefiderocol plasma concentrations were measured using liquid chromatography coupled with the tandem mass spectrometry (LC-MS/MS) approach, through the validated CE-IVD KIT System Antibiotics, by CoQua Lab s.r.l (Turin, Italy) (Mula *et al*., 2023). Plasma quantification was performed on the total concentration of the drugs and the analytical protocol consisted of a fast protein precipitation followed by an ultracentrifugation step. The supernatant was then transferred into a glass vial and injected into the LC-MS/MS System (Triple Quadrupole Xevo TQ-S micro, Waters). Bronchial samples were diluted with Phosphate Buffer Saline (PBS) prior to undergoing the same analytical protocol and measured concentrations were adjusted according to dilution factor.

In our patient, there was a 10-fold increase in cefiderocol concentration on bronchial secretion, according to data available in the literature. In fact, Katsube *et al.* (Katsube *et al*., 2019) studied the pharmacokinetics of cefiderocol in healthy people and found a plasma C_{max} of 142 mg/L and a mean epithelial lining fluid (ELF) concentration of 6.69 mg/L two hours after giving the drug (at a standard dosage in healthy patients). In addition, Kawaguchi *et al.* (Kawaguchi *et al*., 2022) investigated intrapulmonary PK in people who had pneumonia: cefiderocol lung penetration was 1.4 times higher in patients with pneumonia than in healthy people. The authors also reported simulated trough concentrations of cefiderocolat steady state in ELF, reporting in patients with severe renal impairment (cefiderocol dosage of 0.75 g every 12 hours) a C_{trough} at steady state of 9.49 (range 3.81-26.6).

Our group (Mornese Pinna *et al*., 2022) described plasma cefiderocol pharmacokinetics during CVVH in a cohort of critically ill patients, in which the C_{trough} steady state in the three patients described was 57.95 (patient 1), 14.17 (patient 2), and 71.66 mg/L (patient 3). Two of the three patients described were treated for VAP with cefiderocol, but none reported bronchial staining like the one reported in our case. Moreover, we have reported, despite a similar daily dosage of cefiderocol, a two-fold higher cefiderocol concentration in blood. We hypothesize a dose-dependent staining phenomenon of bronchial secretions during cefiderocol therapy, as reported for rifampicin (Grosset, Leventis, 1983; Boeree *et al*., 2017).

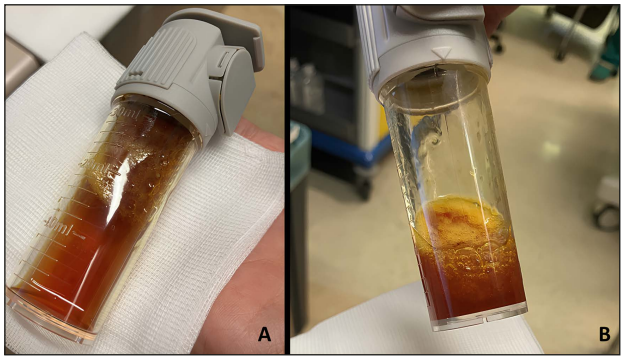

Figure 1 - *Bronchial secretions sampled with fibro-bronchoscopy showing red-brown discolouration.*

Table 1 - *Analysis on bronchial and plasma samples during cefiderocol treatment.*

Variables	*Results*
Bronchial fluid Cefiderocol concentration	71.4 mg/L
Blood Cefiderocol concentration	81.8 mg/L
Chemical examination of bronchial fluids	*RBC* 0.03 cells/mm^3 *WBC* 4.11 cells/mm^3 (PMN 65%) *Hb:* undetectable
Standard culture for bacteria and fungi	Negative
Film-Array Upper e Lower Respiratory Tract	Negative

Abbreviations: RBC: red blood cell; WBC: white blood cell; PMN: polymorphonuclear.

DISCUSSION

Numerous conditions are known to alter the colour of the sputum and bronchial secretions in humans. Bacterial respiratory infections such as *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa* could turn the colour of the sputum green, yellow, yellow-green, or rust. Moreover, acute or chronic airway bleedings are well-known conditions that could change the physiological colouration of bronchial secretions. In our patient, a complete microbiological diagnostic workup turned out negative, and therefore a physical and chemical analysis of BAL fluid showed no airway bleeding and a red blood count of 0.03 cells/mm^3 (*Table 1*). As far as we know, this is the first described case of bronchial secretion staining possibly related to cefiderocol therapy, therefore it is not possible to determine if there are organoleptic characteristics of the secretions that can help in the differential diagnosis for other causes of sputum

staining (i.e., rifampin). More investigations are needed.

Furthermore, recent data showed that urine staining due to cefiderocol is directly and indirectly related to iron body fluid serum concentrations (Lupia *et al*., 2023). The lung is the major organ for gas exchange, and like all other organs, it is exposed to circulating iron (Neves *et al*., 2019). The ability of iron to switch between different oxidation states, specifically between the divalent ferrous (Fe2+) and trivalent ferric (Fe3+) forms of iron, explains its crucial significance (Neves *et al*., 2019). Nevertheless, the chemical characteristic of being a transition metal renders free iron highly reactive and possibly poisonous (Neves *et al*., 2019). Iron acts as a catalyst for the generation of reactive oxygen species (ROS) (Neves *et al*., 2019). The presence of these very reactive radicals leads to the deterioration of lipids, nucleic acids, and proteins, resulting in cellular and, subsequently, tissue harm (Neves *et al*., 2019). Lung inflammation and pulmonary infections lead to higher pulmonary concentrations of free iron and the generation of ROS (Neves *et al*., 2019). In conclusion, due to these data, we hypothesized that higher concentrations of ferric iron in lung tissue, matched with elevated levels of cefiderocol in the blood and bronchial secretions, could theoretically lead to this peculiar clinical manifestation (*Figure 1*). The hypothesis was consistent with cefiderocol-related urine hyperchromia, also recently reported by our group. Clinicians should keep this apparently harmless side effect in mind during cefiderocol treatment.

Although this case report may suggest a correlation between cefiderocol use and staining of bronchoalveolar fluids in humans, more evidence is needed to confirm that these phenomena are statistically associated and, if so, if a causation relationship exists.

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Conflicts of interest

All Authors declare no conflicts of interest.

Availability of data and material

The data presented in this study are available on request from the corresponding author.

Ethics approval

Not requested.

Consent to participate

Not applicable.

Consent for publication

All authors have read and agreed to the published version of the manuscript

We declare that all Authors have seen and approved the manuscript, that they have contributed significantly to the work, and that the manuscript has not been published and is not being considered for publication elsewhere.

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