

Dark Brown Urine in a Patient Treated With Cefiderocol

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Dear Editor,
Numerous drugs are known to alter the colour of urine. Although drug-induced urine staining is normally harmless, it may be frightening to the patient and could lead to unnecessary clinical inquiries. Cefiderocol is a new siderophore cephalosporin antibiotic that binds ferric iron (Fe^{3+}) and uses bacterial iron transporters for intracellular access [1-2].

Cefiderocol is removed often renally as an unmodified drug; nevertheless, urine staining has not been seen at doses used in clinical practice [1]. Recently, Lewis and Arnouk presented a case of dark-red urine discolouration related to the co-administration of cefiderocol and intravenous (IV) ferric gluconate [3].

Iron absorption occurs predominantly in the duodenum and upper jejunum [4]. The mechanism of iron transport from the gut into the bloodstream remains unexplained despite intensive investigation and conclusive evidence [5].

The physical state of iron entering the duodenum significantly influences its absorption. At physiological pH, ferrous iron (Fe^{2+}) is rapidly oxidised to the insoluble ferric (Fe^{3+}) form [4, 5]. Gastric acid reduces the pH in the proximal duodenum, enhancing the solubility and uptake of ferric iron [4-5]. Haem is absorbed by machinery, in contrast to inorganic iron. The process is more efficient and is independent of duodenal pH [4, 5].

Here, we describe the first case of urine chromatu-

ria related to upper gastrointestinal bleeding and the concurrent administration of cefiderocol (Figure 1).

An 82-year-old man with nosocomial pneumonia and rectal colonisation by carbapenem-resistant *Acinetobacter baumannii* was treated with cefiderocol 1.5 g IV every 8 hours, dosed on a chronic kidney failure (GFR 35 mL/min). Seven days into therapy, the patient has worsened due to a gastric ulcer with subsequent massive gastrointestinal bleeding (haemoglobin, 7.0 g/dL; mean corpuscular volume, 91 fL). Subsequently, dark-brown chromaturia was observed after the first few hours of gastrointestinal bleeding, and computed tomography excluded enterovesical fistulae. The patient had a urinary catheter, and his serum creatinine was 1.5 mg/dL with preserved urine output. Urinalysis demonstrated a pH of 6.5 with no red or white blood cells, bilirubin and bacteria. The patient's microbiological urine culture was negative before and after changing the urinary catheter. Liver and muscular enzymes were within normal limits.

Causes of brown urine include food (i.e. fava beans, rhubarb and aloe), medications (i.e. chloroquine, primaquine, metronidazole, nitrofurantoin, senna and methocarbamol) and extreme exercise. In our patient, all these alternative causes have been excluded.

In our patient, urine turned rapidly into a bright yellow 48 hours after discontinuation of cefiderocol. This alteration was observed despite the gastrointestinal bleeding that was treated with medical support. The treatment was administered due to the absence of indications of gastroscopy in consequence of the patient's aggravated condition (Figure 1).

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In cefiderocol dose toxicity studies conducted in animals, chromaturia was observed, including a dose-related false-positive occult blood reaction by urinary test paper [3]. Subsequent studies determined that the change in urine colour was due to renal excretion of cefiderocol–ferric iron complexes under basic conditions [6]. Interestingly, urine pH in our patient was gone alkaline. Furthermore, Conrad et al. showed that iron transport in humans is based on iron-binding proteins at several key sites [7]. They propose that mucins

bind iron in the acid environment of the stomach, thereby maintaining its solution for later uptake in the alkaline duodenum (Figure 2). Their model shows that mucin-bound iron subsequently crosses the mucosal cell membrane in association with integrins. Once inside the cell, a cytoplasmic iron-binding protein called ‘mobilferrin’ accepts the element and shuttles it to the basolateral surface of the cell, where it is delivered to plasma [7]. In the plasma, the iron is coupled with transferrin (Tf) in the circulation which delivers it to the cells

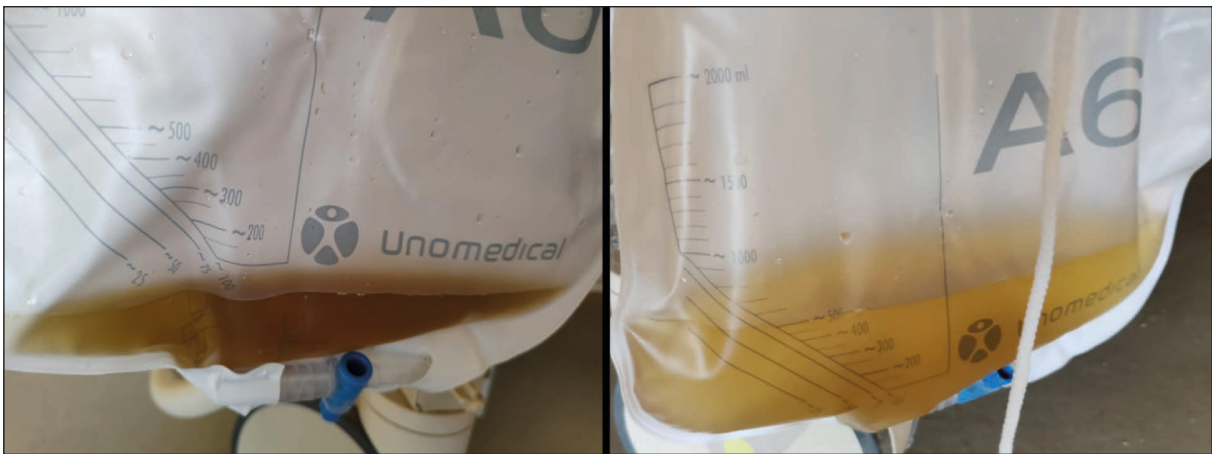
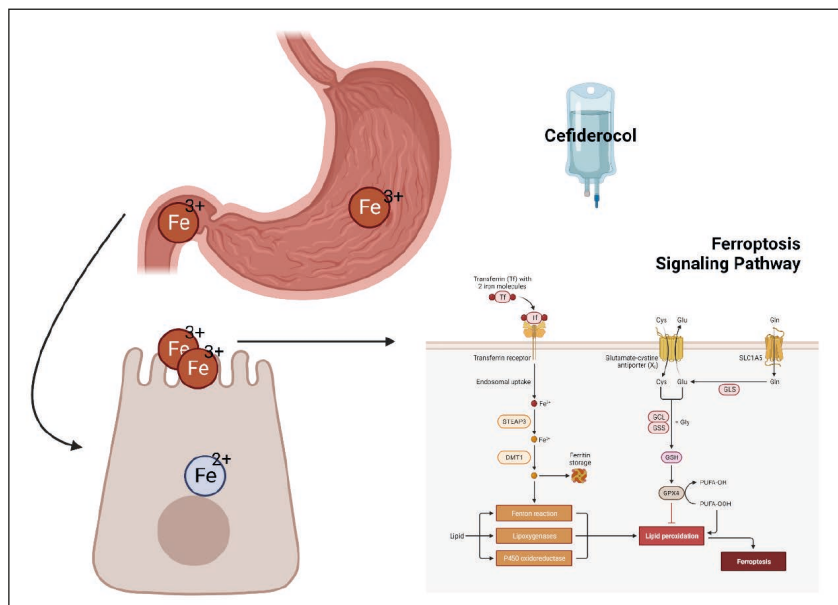


Figure 1 - Urine characteristics during (first box) and 48 hours (second box) after the discontinuation of Cefiderocol despite the gastrointestinal bleeding.

Figure 2 - The basis of Ferroptosis and Cefiderocol entry mechanism (Figure created on www.biorender.com, agreement number: OW25A6L2ZF).



of the body. In our hypothesis, cefiderocol binds an increased amount of re-absorbed iron from the gastrointestinal tract in the ferric form. Although, we consider this condition a benign event as also report by Lewis et al. [3]. Additionally, Skaar et al.'s recent findings showed that baseline serum iron levels did not impact the relative efficacy of cefiderocol versus meropenem in patients with Gram-negative nosocomial pneumonia from the APEKS-NP study data [8].

In summary, we report a novel drug interaction between cefiderocol and high enteral iron repletion due to gastrointestinal bleeding. Further studies may assess whether chromatemia during cefiderocol therapy is an indicator of gastrointestinal bleeding.

Conflict of interest

None to declare.

Funding

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■ REFERENCES

[1] Principe L, Lupia T, Andriani L, et al. Microbiological, clinical, and PK/PD Features of the new anti-gram-negative antibiotics: β -lactam/ β -lactamase in-

hibitors in combination and cefiderocol - an all-inclusive guide for clinicians. *Pharmaceuticals* (Basel). 2022; 15 (4), 463. doi: 10.3390/ph15040463.

[2] Colombo F, Waheed A, Panese So, et al. Treatment with cefiderocol in *K. pneumoniae* KPC nosocomial external ventricular drainage meningitis: A brief report. *Infez Med.* 2022; 30 (3), 454-458.

[3] Lewis TC, Arnouk S. Dark Red Urine in a Patient on Cefiderocol and Ferric Gluconate. *Ann Pharmacother.* 2022 Jan 6, 10600280211070029. doi: 10.1177/10600280211070029.

[4] Muir A, Hopfer U. Regional specificity of iron uptake by small intestinal brush-boarder membranes from normal and iron deficient mice. *Am J Physiol.* 1985; 11, 6376-6379.

[5] Andrews NC. Intestinal iron absorption: current concepts circa 2000. *Dig Liver Dis.* 2000; 32 (1), 56-61.

[6] European Medicines Agency. Fetroja. https://www.ema.europa.eu/en/documents/assessment-report/fetroja-epar-public-assessment-report_en.pdf. Published February 27, 2020.

[7] Conrad ME, Umbreit JN. A concise review: Iron absorption - the mucin-mobilferrin-integrin pathway. A competitive pathway for metal absorption. *Am J Hematol.* 1993; 1003: 42, 67.

[8] Skaar EP, Echols R, Matsunaga Y, Menon A, Portsmouth S. Iron serum levels and iron homeostasis parameters in patients with nosocomial pneumonia treated with cefiderocol: post hoc analysis of the APEKS-NP study. *Eur J Clin Microbiol Infect Dis.* 2022; 41 (3), 467-476. doi: 10.1007/s10096-021-04399-9.