Septic shock due to meropenem- and colistin-resistant Cupriavidus pauculus

SEPTIC SHOCK DUE TO MEROPENEM AND COLISTIN RESISTANT CUPRIAVIDUS PAUCULUS

Bianco Gabriele[1]*, Boattini Matteo[1]*, Audisio Ernesta[2], Cavallo Rossana[1], Costa Cristina[1]

* These authors contributed equally to this work

Affiliations:

[1] Microbiology and Virology Unit, University Hospital Città della Salute e della Scienza di Torino, Turin, Italy

[2] Ematology, Department of Hematology and Oncology, University Hospital Città della Salute e della Scienza di Torino, Turin, Italy

Corresponding author:

Matteo Boattini, Microbiology and Virology Unit, University Hospital Città della Salute e della Scienza di Torino, Corso Bramante 88, 10126, Turin, Italy; Tel. +39 011 6335948; matteo.boattini@edu.unito.it

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Dear Sir,

the Sepsis-3 defines sepsis as a life-threatening organ dysfunction due to dysregulated host response to infection. Septic shock occurs in patients with sepsis and it is a high mortality acute syndrome characterized by impaired distribution of microvascular blood flow and cellular dysoxia. It is defined by persisting hypotension requiring vasopressors to maintain a mean arterial blood pressure (BP) greater than 65 mmHg and a serum lactate level greater than 2 mmol/L despite adequate volume resuscitation.

The genus *Cupriavidus* refers to an ubiquitous, Gram-negative, aerobic, non fermenting, non spore forming bacilli tipically distributed in environmental habitats. *Cupriavidus pauculus* has been implicated in the majority of the infections [1] but few cases are reported in the literature.

In November 2017, a 48-year-old woman with obesity and hypertension was referred to our hospital because of a diagnosis of acute myelomonocytic leukemia.

A central line was placed and a chemotherapy regimen 7+3 with Cytarabine/Idarubicin was started.

On hospital day 9 the patient became hypotensive, tachycardic, tachypneic, febrile and oligoanuric. Blood gas analysis showed compensated metabolic acidosis and hyperlactacidemia. Biochemistry was consistent with aplastic phase following chemotherapy. Due to maintain a mean BP lower than 65 mmHg after crystalloid resuscitation, norepinefrine was started.

Two pairs of aerobic and anaerobic blood cultures, drawn through the central venous catheter, were performed and Meropenem (1 g every 8 h), Vancomycin (1 g every 12 h) and Caspofungin (50 mg every 24 h) were started.

After 24 h, Gram staining showed gram negative rods in the aerobic blood cultures. Vancomycin and Caspofungin were stopped and the central line was removed.

After 48 h, round and smooth colonies, catalase and oxidase positive grew on blood agar plates and non-lactose-fermenter colonies grew on MacConkey agar plates. Microscan Walkaway 96 Plus (Beckman Coulter) and Phoenix (Becton Dickinson) automated system were not able to identify the isolated agent.

Identification of *C. pauculus* (confidence values of 99.9%) was performed with Matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (VITEK MS system- BioMérieux).

The isolate subsequently underwent 16S rRNA gene sequencing that identified *C. pauculus* (100% match with *C. pauculus* strain CIP 105943, GenBank accession no NR 116147).

The *in vitro* susceptibility of the isolate was assessed with Etest. Colistin was tested by means of a broth microdiluition system. Results are reported in the Table.

Following the results of susceptibility testing, Ciprofloxacin (400 mg every 12 h) was added to Meropenem and antimicrobial therapy was continued for 10 days. We decided to add Ciprofloxacin to Meropenem because we are not comfortable with suspending Meropenem and de-escalate antimicrobial therapy due to possibility of undetected coinfection.

Molecular genetic assay did not identify carbapenemase genes KPC, OXA, VIM, IMP, NDM.

Patient was discharged on day 28 in good clinical condition and she is still being followed in Hematology out-patient clinic.

In order to avoid *C. pauculus* outbreaks, enviromental survey was performed in the wards to which the patient had been admitted and it was negative.

Previously known as CDC group IVc-2, *Ralstonia* and later *Wautersia*, the genus *Cupriavidus* contains 13 species. *C. pauculus* can induce infection in

immunocompromised as well as in immunocompetent individuals, in community or nosocomial setting. It can cause bacteremia, pneumonia, meningitis, intravascular catheter and medical devices bloodstream infections [1-8].

The incidence of *Cupriavidus spp*. infections may be underreported due to misidentification on actual automated laboratory platforms.

Recent introduction of MALDI-TOF mass spectrometry improved the possibilities to phenotypically identify this unusual pathogen.

Few data are reported about antimicrobial susceptibility. Wide susceptibility to fluoroquinolones, Ceftazidime and Imipenem had been observed [1].

Resistance to Carbapenems had been described. Karafin *et al.* reported a case of Meropenem and Imipenem resistant *C. gilardii* bacteremia [6]. Salar *et al.* described a case of Imipenem resistant *C. pauculus* bacteremia [7]. Uzodi *et al.* reported a Meropenem resistant *C. pauculus* bacteremia in a child on extracorporeal membrane oxygenation [2]. Few data about Colistin minimal inhibitory concentration (MIC) are reported too. Aydin *et al.* [3] and Dan *et al.* [8] described two cases with Colistin susceptibility. Conversely, Vay *et al.* [4] reported a Meropenem and Imipenem susceptible *C. pauculus* bacteremia with Colistin MIC 2 µg/mL.

Optimal regimen for therapy of *C. pauculus* is not known and specific clinical breakpoints are lacking. D'Inzeo *et al*. [1] and Langevin *et al.* [5] interpreted *C. metallidurans* susceptibility according to Clinical and Laboratory Standards Institute (2013) breakpoints for *Pseudomonas aeruginosa*. According to *Pseudomonas spp.* European Committee on Antimicrobial Susceptibility Testing Clinical Breakpoint (2018) *C. pauculus* strain isolated in our patient is resistant to Meropenem (MIC Breakpoint: R >2) and Colistin (MIC Breakpoint: R >2).

We report the first case of septic shock caused by Meropenem and Colistin resistant *C. pauculus.*

C. pauculus is able to cause severe infections in humans and to easily gain antimicrobial resistance presenting a susceptibility profile not far to a multidrug resistant agent.

Conflict of interest:

All authors report no conflicts of interest.

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