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Shunt lock therapy with micafungin to treat shunt-associated *Candida albicans* meningitis in an infant

Cinzia Auriti[1]*, Fiammetta Piersigilli[1], Maria Paola Ronchetti[1], Francesca Campi[1], Paolina Giuseppina Amante[2], Marco Falcone[3] and Bianca Maria Goffredo[4]

[1]*Neonatal Intensive Care Unit, Department of Neonatology, Bambino Gesu' Children's Hospital, Rome, Italy;* [2]*Neurosurgery Unit, Department of Neurosurgery, Bambino Gesu' Children's Hospital, Rome, Italy;* [3]*Infectious Diseases Section, Department of Public Health and Infectious Diseases, 'La Sapienza' University, Rome, Italy;* [4]*Laboratory of Biochemistry, Department of Specialist Pediatrics, Bambino Gesù Children's Hospital, Rome, Italy*

*Corresponding author. Neonatal Intensive Care Unit, Department of Neonatology, Onofrio No. 4, Bambino Gesù Children's Hospital, Piazza S. Onofrio No. 4, 00165 Rome, Italy. Tel: +390668592427; E-mail: cinzia.auriti@opbg.net

Sir,

Shunt-associated fungal infections are currently treated with systemic antifungal therapy and shunt replacement, as fungi inside the lumen form a biofilm in which microorganisms are protected from antifungal therapy. This is the reason why CSF cultures may remain positive despite optimal therapy.[1] Echinocandins may eliminate fungal biofilms from central vascular catheters (CVCs).[2] Antifungal 'lock therapy' (LT), consisting of high concentrations of the drug instilled into the lumen of the catheter and left in place for few hours, has been suggested as a possible therapeutic option for CVC-related fungal infections when catheter removal is difficult or dangerous in critically ill patients.[3] There are no publications concerning this approach in patients with brain external ventricular drain (EVD)-associated fungal meningitis.

We successfully treated a shunt-associated *Candida albicans* meningitis with systemic antifungal therapy combined with micafungin LT of the EVD in a seriously ill, preterm infant.

A 1490 g, 29 week male infant developed intraventricular haemorrhage grade IV on day 2 of life (DOL) and at 25 DOL was referred to our Neonatal Intensive Care Unit for hydrocephalus requiring neurosurgery. He promptly underwent EVD and subsequently ventricular–peritoneal (VP) shunt placement. After 1 month the VP shunt had to be replaced by an EVD because of onset of *Staphylococcus epidermidis* bloodstream infection and meningitis. At 5 months the infant developed a catheter-related *C. albicans* bloodstream infection. The *Candida* isolate was susceptible to fluconazole, 5-flucytosine, amphotericin B, anidulafungin, caspofungin and micafungin. The CVC was replaced and therapy was started with intravenous micafungin at a dosage of 15 mg/kg/day for 3 days consecutively followed by 10 mg/kg/day. The CSF examination documented a high white blood cell count (1400 cells/mm^3), elevated proteins (300 mg/dL) and low glucose (<1 mg/dL) and CSF cultures grew the same *C. albicans* strain. Intravenous 5-flucytosine at a dose of 100 mg/kg twice daily was added to the systemic therapy and the EVD was removed and also replaced in the same session. CSF and plasma levels of micafungin were determined by HPLC (Table 1). Because CSF cultures remained positive we decided to perform LT with micafungin for 2 days consecutively. We instilled inside the EVD 1.1 mL (equal to the priming volume of the catheter) of a solution containing 1.5 mg/L micafungin sodium in sterile water (100-fold higher than *Candida* MIC), closing the EVD for 6 h (the drug's stability in sterile water had been previously tested by HPLC serial dosages). Then the lock content was aspirated. Systemic therapy was continued. We finally obtained sterilization of the CSF without having to remove the EVD and no recurrence of *Candida* CSF infection was observed.

To our knowledge, this is the first report of a persistent shunt-associated *Candida* meningitis successfully treated with a combined therapy with a systemic high dose of antifungal therapy plus micafungin EVD LT.

Very low birthweight neonates and infants born preterm may require higher doses of some drugs, included micafungin (from 7 to 15 mg/kg/day in neonates versus 1–4 mg/kg/day in adults), because of greater drug clearance.[4] Regarding micafungin, studies suggest that binding of the drug to plasma proteins is ~8-fold lower in neonates than in adults, causing an increase in the proportion of free drug that can be rapidly eliminated.[5,6] Therefore, questions arise about which is the appropriate dose to ensure therapeutic levels of the drug, especially in CSF infections.[7,8]

Table 1. Plasma, CSF and steady-state (2–8 h) micafungin concentrations (mg/L) at two dosages

Dose (over 24 h)	Site	Pre-infusion	Time after infusion			Steady-state[a] mean (range)
			30 min	2 h	8 h	
15 mg/kg	plasma	5.8	21.9	17.9	13.2	15.5 (13.2–17.9)
	CSF	0.8	0.9	1.1	0.8	0.9 (0.8–1.1)
10 mg/kg	plasma	6.7	17.4	13.2	8.9	11.1 (8.9–13.2)
	CSF	0.3	0.4	0.5	0.3	0.4 (0.3–0.5)

Plasma and CSF samples were drawn simultaneously at different timepoints after the end of the intravenous infusion.
Note that CSF concentrations of micafungin were higher than the *Candida albicans* micafungin MIC (0.015 mg/L), at both drug dosages.
[a]Steady-state concentrations were measured 2–8 h after dosing.

Using an initial micafungin dose of 15 mg/kg/day and then 10 mg/kg/day, we were able to obtain high plasma concentrations, achieving a plasma C_{max}/MIC ratio significantly higher than 10. As expected, the mean concentration was significantly lower in CSF than in plasma at the same time of sampling (Table 1). However, CSF concentrations ranging between 0.0188 and 4.66 mg/L are considered effective.[7] Moreover, in our patient CSF micafungin concentrations were significantly higher than the *C. albicans* micafungin MIC (0.015 mg/L) with doses of 15 and 10 mg/kg/day, and were adequate to reach a C_{max}/MIC ratio >10. We also added 5-flucytosine to the systemic therapy, a drug able to penetrate the CSF, to obtain sterilization. We speculate that the persistence of *Candida* CSF infections was likely caused by intraluminal early colonization with *C. albicans*, reducing the effectiveness of the ongoing therapy. We therefore added EVD LT with micafungin to systemic therapy to hinder biofilm formation, giving time for the intravenous therapy to act. Further research is necessary to determine the appropriate duration and the number of locks required to achieve catheter sterilization when replacement is contraindicated, or to prevent recolonization after new EVD insertion. Nonetheless, to perform LT of the EVD with micafungin in conjunction with systemic therapy might be used as a rescue treatment to prevent early re-colonization of the catheter and the persistence of *Candida* infection in shunt-associated meningitis.

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This study was carried out as part of our routine work.

Transparency declarations

All authors have none to declare.

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