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Case Report

Cyberlindnera fabianii in the neonatal and paediatric intensive care unit: case reports

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Introduction: The number of infections due to uncommon yeast species is gradually increasing worldwide. In cases of high-risk paediatric patients, *Cyberlindnera fabianii* has been identified as the causal agent in a number of countries. In fact, we have recently reported the first proven occurrence, to the best of our knowledge, of this species as a causal agent of fungaemia in three neonatal patients in a Croatian hospital.

Case presentation: We report here six new instances of clinically manifested bloodstream and urinary tract infections caused by *Cyberlindnera fabianii* in five high-risk neonates and one child, during a 5-year period (2008–2012) in the aforementioned Croatian hospital. In addition, we have provided an account of their treatment strategy and the outcome, and the susceptibility profiles of 44 isolates of *Cyberlindnera fabianii* to amphotericin B, flucytosine, triazoles and echinocandins. Furthermore, we have described a novel molecular method suitable for the rapid and specific diagnosis of this species.

Conclusion: Our findings demonstrated: (i) the pathogenic activities of *Cyberlindnera fabianii* species in high-risk children; (ii) that administering fluconazole either prophylactically or therapeutically yielded no results in 50 % of the patients; (iii) that substituting fluconazole by liposomal amphotericin B or caspofungin managed to resolve sepsis in the remaining 50 % of patients; (iv) that, according to the examined sequences, all of the *Cyberlindnera fabianii* isolates were found to be identical independent of their source or study period; and (v) the existence of a higher proportion of non-susceptible isolates of *Cyberlindnera fabianii* for echinocandins (especially micafungin) compared with the other tested antifungals.

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Introduction

Infections caused by rare *Candida* spp. have become increasingly common in high-risk patients within hospital settings (Valenza *et al.*, 2006; Wu *et al.*, 2013). Among these, *Cyberlindnera fabianii*, the teleomorph of *Candida fabianii* (Freel *et al.*, 2014), has been reported by a few researchers as the causative agent of various infections (Bhally *et al.*, 2006; Valenza *et al.*, 2006; Gabriel *et al.*, 2012; Wu *et al.*, 2013; Yun *et al.*, 2013). In addition, we have previously described three cases of clinically manifested fungaemia in neonatal patients caused by *Cyberlindnera fabianii*[Q1], initially misidentified as *Candida utilis* (Lukić-Grlić *et al.*, 2011). From 2008 to 2012, *Cyberlindnera fabianii* was isolated from various clinical samples of another six patients hospitalized in the neonatal intensive care unit (NICU) and paediatric intensive care unit

Abbreviations: CASPO, caspofungin; CRP, C-reactive protein; CVC, central venous catheter; ELBW, extremely low birth weight; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FLU, fluconazole; ICI, invasive *Candida* infection; i.v., intravenous; IAMB, liposomal amphotericin B; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.

The GenBank/EMBL/DDBJ accession numbers for the *Cyberlindnera fabianii* sequences determined in this study are KM384023–KM384033.

(PICU) of our hospital (Children's Hospital Zagreb, Zagreb, Croatia). The sporadic occurrence of this yeast over a longer period (5 years) in an increased number of patients was the reason for the detailed analysis and the subsequent presentation of clinical, diagnostic, prophylactic and therapeutic data.

Case report

Case 1

The patient was a 3-and-a-half-year-old girl hospitalized in the PICU of the Children's Hospital in Zagreb, in the autumn of 2008, 5 months after receiving her last cycle of chemotherapy for acute lymphoblastic leukaemia. She was admitted to the hospital with high fever, a high C-reactive protein (CRP) level and a low white blood cell count. Extended-spectrum antibiotic therapy commenced (without any detected micro-organisms) and after 5 days fluconazole (4 mg kg^{-1} orally) was added to the treatment. On day 20 of hospitalization, the patient's condition worsened (fever of 38.5 °C accompanied by chills and vomiting). Laboratory findings manifested an elevated level of CRP (24 mg l^{-1}) and mild thrombocytopenia ($70 \times 10^9\ l^{-1}$). A non-*albicans Candida* sp. was isolated from blood culture, as well as from a stool sample. The fluconazole dosage was increased to 6 mg kg^{-1} intravenously (i.v.). As the blood culture taken 5 days later was still positive for the same yeast, fluconazole was substituted with liposomal amphotericin B (3 mg kg^{-1}) (Table 1). After 3 days of amphotericin B therapy, there was a noticeable clinical improvement and the blood culture became sterile. The same therapy was continued for a further 11 days.

Case 2

In November 2009, a 1.5-month-old male infant was admitted to our hospital with bilateral hydronephrosis, vesicoureteral reflux grade IV and a posterior urethral valve. Ten days after his arrival, he was transferred to PICU due to urosepsis. Extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* was isolated only from the urine sample, warranting the introduction of meropenem (20 mg kg^{-1}) to the therapy. A control urine sample taken a few days later tested positive for non-*albicans Candida* sp. Fluconazole (6 mg kg^{-1} orally) was added to the therapy and he was transferred to the Department of Urology. After another 5 days, the patient became febrile with a CRP level of 21 mg l^{-1} and white blood cell count of $14.6 \times 10^9\ l^{-1}$, and he was again admitted to the PICU. The same yeast species was again isolated from a urine sample, and fluconazole (6 mg kg^{-1}) was given intravenously. After 48 h, clinical stabilization was brought about, prompting a surgical operation the next day (resection of the posterior urethral valve and suprapubic Cystofix cystostomy). The last positive urine sample was taken on day 8 after surgical treatment. Fluconazole was administered for a total of 27 days (Table 1).

Table 1. Clinical and microbiological data on the six presented cases *of Cyberlindnera fabianii* infections

Case no.	Age/sex	Predisposing factors	Episode	Specimen and no. isolates/year of isolation	Prophylaxis/treatment	Clearance time*	Outcome
1	3.5 years/F	Leukaemia, neutropenia, antibacterial therapy	Fungal sepsis	Blood 2, stool 1/2008	FLU/FLU for 5 days, then lAMB for 14 days	3 days	Resolved
2	2 months/M	Hydronephrosis, surgery, antibacterial therapy	Fungal urosepsis	Urine 3/2009	–/FLU 27 days, urinary catheter removal	11 days	Resolved
3	Neonate/F	Gastroschisis, surgery, mechanical ventilation, parenteral nutrition, antibacterial therapy	Fungal urosepsis	Urine 1, nasopharyngeal swab 2/2011	–/FLU for 27 days, urinary catheter removal, CVC removal	5 days	Resolved
4	Neonate/M	Hydronephrosis, surgery, parenteral nutrition, antibacterial therapy	Fungal urosepsis	Urine 13, ureostomal swab 8, wound 1, stool 1, air samples 2/2011	–/FLU for 30 days, then CASPO for 10 days	10 days	Resolved
5	Neonate/F	Intestinal atresia, surgery, parenteral nutrition, antibacterial therapy	Fungal sepsis	Blood 2, stool 1, gastric content 1/2012	FLU/FLU for 15 days, CVC removal	7 days	Resolved
6	Neonate/F	Pulmonary cyst, 740 g weight, antibacterial therapy, mechanical ventilation, parenteral nutrition	Fungal severe sepsis	Blood 3, tubal aspirate 2, oropharyngeal swab 1/2012	FLU/FLU for 2 days, then CASPO for 21 days	7 days	Resolved

[Q4]F, female; M, male; FLU, fluconazole; lAMB, liposomal amphotericin B; CASPO, caspofungin.
*Clearance time from the bloodstream or urinary tract after introducing the last antifungal drug.

Case 3

In May 2011, a female newborn with a birth weight of 3470 g, born in week 38 of gestation, was hospitalized in the NICU with gastroschisis. Operative treatment commenced on the same day, beginning with antibiotic prophylaxis (ampicillin and gentamycin). The day after she became febrile, her CRP level increased to 123 mg l^{-1}. Blood cultures were taken, and gentamycin was replaced with meropenem (20 mg kg^{-1}) along with the addition of metronidazole. Blood cultures proved to be sterile. On day 12 of hospitalization, the symptoms of sepsis developed again with a CRP level of 101 mg l^{-1}. Blood cultures, urine samples and nasopharyngeal aspirate were taken; the central venous catheter (CVC) was removed, and vancomycin, piperacillin-tazobactam and fluconazole (6 mg kg^{-1} i.v.) were added to the therapy. Blood cultures and the nasopharyngeal aspirate were positive for *Chryseobacterium indologenes*. Non-*albicans Candida* sp. was isolated from the urine and aspirate samples. Subsequently, the same dose of fluconazole was continued (6 mg kg^{-1} i.v.) for a period of 27 days (Table 1). A urine sample taken on day 17 of hospitalization was sterile.

Case 4

A male newborn weighing 2900 g, born in week 36 of gestation, was hospitalized in the NICU with bilateral ureterohydronephrosis, a posterior urethral valve and vesicoureteral reflux grade IV in October 2011. On day 10 of hospitalization, he became septic. Blood cultures and urine were taken, and antibiotic therapy (meropenem) was started. Non-*albicans Candida* sp. was isolated only from the urine sample. Fluconazole at a reduced dose (3 mg kg^{-1} i.v., because of decreased renal function) was applied. On day 15 of hospitalization, due to the progression of ureterohydronephrosis, the surgical procedure of ureterocutaneostomy had to be performed. During the next 3 weeks, in spite of fluconazole therapy, we were able to collect 24 more non-*albicans Candida* sp. isolates from different clinical and environmental samples (Table 1). During that time, screening tests for dissemination of fungal infection proved negative, so the fluconazole therapy was continued for 30 days in total. On day 45 of his life, he was septic again; his CRP level was 31 mg l^{-1} and white blood cell count was 14.27×10^9 l^{-1}. As the same yeast persisted in the urine samples, a reduced dosage of caspofungin (1.0 mg kg^{-1} i.v.) was applied for the next 10 days (Table 1) until the urine became sterile.

Case 5

In September 2012 a female neonate (40 weeks of gestation, 3730 g of body weight) was hospitalized in the NICU after undergoing a surgical procedure due to an intestinal atresia. She was on parenteral nutrition and anti-ulcer prophylaxis, and was receiving antibiotic therapy (ampicillin and gentamycin for 6 days). Because of the presence of extended-spectrum β-lactamase-producing *K. pneumoniae* in nasopharyngeal swab and stool samples, the initial antibiotic therapy was [Q2]changed to meropenem. On day 5 of hospitalization in the NICU, non-*albicans Candida* sp. was isolated from the stool and gastric content, and fluconazole (6 mg kg^{-1} i.v.) was introduced to the therapy. On day 22, she became septic, with a fever of 38.7 °C and CRP level of 30 mg l^{-1}. Non-*albicans Candida* sp. and meticillin-resistant *Staphylococcus epidermidis* were isolated from two blood cultures obtained on the same day. As a result, the CVC was removed, whilst vancomycin (15 mg kg^{-1}) every 6 h for 7 days and fluconazole (12 mg kg^{-1} i.v.) for 15 days were applied (Table 1).

Case 6

In September 2012, at the same time as the patient described in case 5, a female premature infant, born after 24 weeks of gestation and with an extremely low birth weight (ELBW) of 740 g, was admitted to our NICU on day 10 of her life because of a large cyst in her lungs. Upon admittance, she was already on antibiotic therapy (ampicillin and gentamycin) and antifungal prophylaxis (fluconazole 5 mg kg^{-1} i.v. every 72 h). On day 25, after the cessation of fluconazole prophylaxis, a non-*albicans Candida* sp. was isolated from the aspirate of an endotracheal tube. Fluconazole (6 mg kg^{-1} i.v. every 48 h) was again instituted as therapy, but after 2 days the infant's fever rose drastically to 38.5 °C, her CRP level increased to 30 mg l^{-1} and the thrombocyte count decreased to 45×10^9 l^{-1}. Blood cultures, as well as other clinical specimens, were taken for bacteriological and mycological examination. The same yeast was isolated from three blood cultures (on alternate days over a 5-day span) and from the oral cavity. Fluconazole was replaced with caspofungin (2 mg kg^{-1}) for the next 3 weeks (Table 1).

Investigations

In vitro antifungal susceptibility testing was performed using the ATB FUNGUS 3 (bioMérieux,) microdilution method, and the results were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations. No *in vitro* resistance to amphotericin B, flucytosine, fluconazole, itraconazole or voriconazole was observed. Of the three echinocandins, only caspofungin was available in Croatia during the observed period (anidulafungin was registered in 2013 and micafungin in 2014); however, EUCAST breakpoints had not yet been established for caspofungin. Therefore, the susceptibility testing of all isolates for echinocandins was done later using Etest (Liofilchem). MIC values showed variation among the isolates to a certain degree; however, they were the lowest for anidulafungin (0.016–0.064 mg l^{-1}), higher for caspofungin (0.125–0.19 mg l^{-1}) and highest for micafungin (1–4 mg l^{-1}).

Diagnosis

A total of 44 isolates were recovered from various specimens of the six patients on Sabouraud glucose agar (Tables 1 and 2) and were ultimately identified using an API ID 32C kit (bioMérieux) and on the basis of cornmeal agar morphology as *Candida utilis*.

The identity of 11 selected isolates was checked by the PCR amplification, sequencing and sequence analysis of a fragment of the rRNA gene region (Kocsubé *et al.*, 2007) (Table 2). Amplification was performed using the universal primers ITS1 and ITS4 (White *et al.*, 1990) targeting the internal transcribed spacer (ITS) of the ribosomal gene cluster. Based on the sequence data, all 11 isolates were re-identified as *Cyberlindnera fabianii* (Table 2). Phylogenetic reconstruction was conducted using raxmIGUI v.1.3 under the GTR + G model (Silvestro & Michalak, 2011). The analysis was run with 1000 bootstrap replicates. The ITS sequences of the isolates were found to be identical, showing no genetic differences among the strains (Fig. 1). Based on a species-specific sequence of the rRNA gene region of *Cyberlindnera fabianii*, a species-specific primer (5′-TGCGTGGAATAAGCCTAGCT-3′) was designed to be used in combination with the common ITS4 primer for identification of the rest of the isolates. The reaction mixture contained 2 µl 10 × *Taq* buffer with KCl (Thermo Scientific), 2 µl $MgCl_2$ (25 mM), 4 µl dNTP mix (2 mM each), 4 µl of each primer (1 µM each), 3 µl ddH_2O, 0.1 µl *Taq* DNA polymerase (5 U μl^{-1}) and 1 µl template DNA. An approximately 510 bp fragment was amplified using one cycle of 94 °C for 3 min, 35 cycles of 94 °C for 20 s, 48 °C for 15 s and 72 °C for 40 s, and one cycle of 72 °C for 2 min. The newly developed PCR-based method proved to be suitable for the rapid and specific detection and identification of *Cyberlindnera fabianii*. With this new approach, the identity of all the isolates reported in this study was confirmed as *Cyberlindnera fabianii* (Fig. 2).

Table 2. GenBank accession numbers of the ITS sequences of *Cyberlindnera fabianii* isolates from the presented cases

Case	Isolate	Origin	GenBank accession number
1	CfZg 10	Stool	KM384032
2	CfZg 17	Urine	KM384031
3	CfZg 20	Nasopharyngeal swab	KM384030
4	CfZg 25	Left urostoma	KM384029
4	CfZg 26	Wound around left urostoma	KM384028
4	CfZg 32	Air above the child	KM384027
4	CfZg 33	Air inside the respirator	KM384026
4	CfZg 45	Right urostoma	KM384025
5	CfZg 51	Gastric content	KM384024
6	CfZg 52	Tubal aspirate	KM384023
6	CfZg 55	Swab of buccal cavity	KM384033

Discussion

We have presented the cases of six patients who were hospitalized in the NICU and PICU over a period of 5 years (2008–2012) with *Cyberlindnera fabianii* isolated from various clinical specimens.

Cyberlindnera fabianii has been described as a causative agent of infections both in infants and adults (Bhally *et al.*, 2006; Valenza *et al.*, 2006; Gabriel *et al.*, 2012; Wu *et al.*, 2013). Using commercial yeast diagnostic kits, such as API 20C AUX, ID32C and Vitek-2, these isolates have frequently been misidentified (Valenza *et al.*, 2006; Gabriel *et al.*, 2012). After three incidences of *Candida utilis* candidaemia in our NICU in 2008 (Lukić-Grlić *et al.*, 2011), 42 other isolates were collected from six other patients with fungaemia or funguria, along with two environmental specimens. All isolates were re-identified as *Cyberlindnera fabianii* (teleomorph of *Candida fabianii*) by analysis of their ITS sequences, as well as by the novel, PCR-based technique described above. This method proved to be suitable for rapid and specific diagnosis, verifying in turn that all of the examined *Cyberlindnera* isolates belonged to this uncommon species.

The process of predicting possible risks for patients in the NICU and PICU of developing invasive *Candida* infections (ICI) poses a crucial challenge. By combining various risk factors, it has been shown that the risk of ICI in these patients ranges from 10 to 46 % (Zaoutis *et al.*, 2010; Brissaud *et al.*, 2012). All of our six patients had different risk factors: one was a premature infant with ELBW (< 1000 g), another one was a child with leukaemia and neutropenia, three of them underwent surgical procedure, and all were on parenteral nutrition and antibiotic therapy (Table 1). There are around 400 patients hospitalized in our hospital's PICU every year, whilst 50 patients get admitted to the NICU. During the described period, the incidence of ICI in the NICU was 4 %, whilst it was only 0.5 % in PICU patients. The most often detected causative agent in NICU patients was *Cyberlindnera fabianii* followed by *Candida albicans*, whereas *Candida albicans* was the leading causative agent of ICI in the PICU. Decisions for implementing antifungal prophylaxis were made on an individual basis so that ultimately three of our patients received it (Table 1). After the isolation of *Cyberlindnera fabianii*, fluconazole therapy was initiated, whilst liposomal amphotericin B was continued in one patient and caspofungin in the remaining two (Table 1). From 2013 until now, the yearly incidence of ICI in the NICU has been reduced to 2 %. Whilst *Candida guilliermondii* caused the only case of ICI in 2013, *Candida albicans* was responsible for the single ICI in 2014.

Candidaemia in children caused by *Cyberlindnera fabianii* has been described in a few publications (Bhally *et al.*, 2006; Hamal *et al.*, 2008; Grenouillet *et al.*, 2010; Lukić-Grlić *et al.*, 2011; Wu *et al.*, 2013). In this paper, we present not only three more cases of fungaemia but also three cases of funguria caused by *Cyberlindnera fabianii*. Until now,

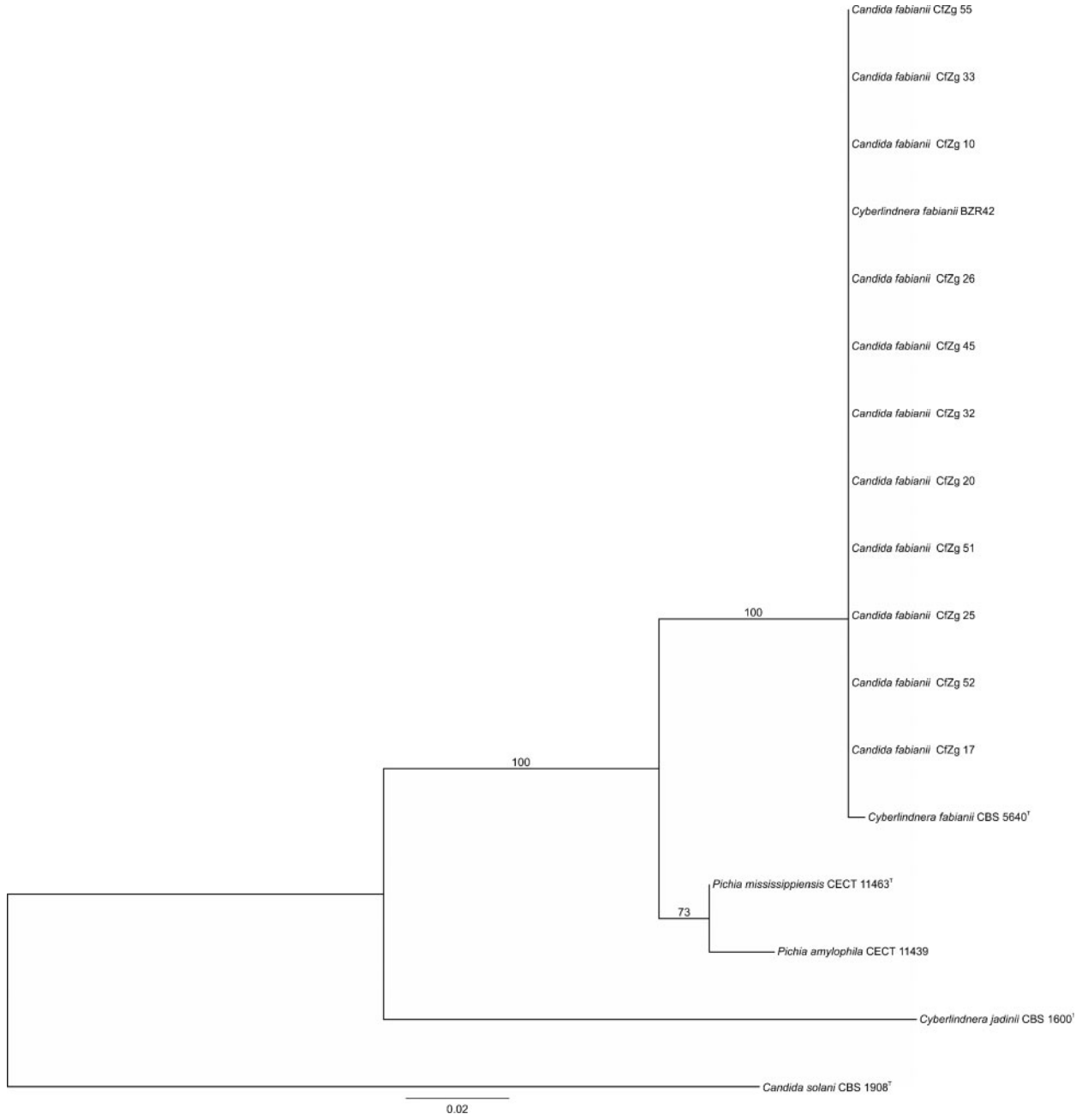

Fig. 1. Maximum-likelihood tree based on the ITS sequences of *Cyberlindnera/Candida fabianii* isolates reported in the present study. Numbers above branches are bootstrap values. Only values above 70 % are indicated.

there has only been one paper, to the best of our knowledge, reporting *Cyberlindnera fabianii* candiduria (presented as prostatitis) in a 57-year-old male patient with chronic lymphatic leukaemia (Dooley *et al.*, 1990). In critically ill children, urinary tract abnormalities, use of a urinary catheter, prior dialysis, total parenteral nutrition, use of a vascular catheter, artificial ventilation and duration of therapy with broad-spectrum antibiotics are associated with candiduria (Trnka *et al.*, 1998). According to the literature, candiduria develops in approximately 2.4 % of very low birth weight ($<$1500 g) infants and up to 6 % of ELBW ($<$1000 g) infants (Kaufman & Fairchild, 2004).

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend fluconazole prophylaxis for the prevention of ICI in neonates, whilst for therapeutic options they propose various formulations of amphotericin B, fluconazole, caspofungin and micafungin

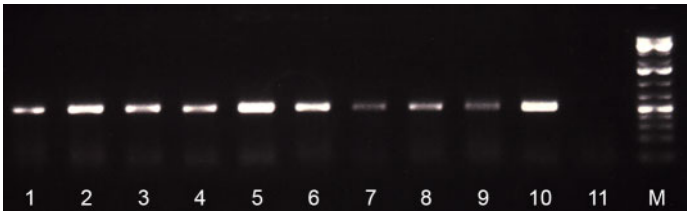

Fig. 2. Electrophoretic photograph of the amplicons obtained in the reaction specific for *Cyberlindnera fabianii*. Lanes 1–10, *Cyberlindnera fabianii* isolates, lane 11, *Candida utilis*; lane M, 1 kb DNA ladder.

(Hope *et al.*, 2012). Among our patients, the prophylactic application of fluconazole was not successful in preventing ICI. However, fluconazole treatment (with removal of the CVC and/or urinary catheters) or substituting fluconazole with liposomal amphotericin B or caspofungin led to clinical resolution and elimination of *Cyberlindnera fabianii* from the blood or urine (during the time of the treatment, micafungin had not yet been registered in Croatia).

The attributable mortality of candidaemia in children has been reported to be 10 % (Zaoutis *et al.*, 2010). Grenouillet *et al.* (2010) described a case of *Cyberlindnera fabianii* candidaemia in an ELBW pre-term infant with a fatal outcome. Rather limited information can be found in the literature pertaining to the prognosis of candidal urinary tract infections in infants in the NICU. Robinson *et al.* (2009), in a study of the characteristics and outcome of infants with candiduria, found the mortality of 30 % to be linked with *Candida* infection, suggesting the need for antifungal therapy with repeated evaluation for dissemination in those infants who are slow to respond to therapy. Studies have demonstrated a similar mortality rate in infants with *Candida* urinary tract infection alone (26 %), compared with *Candida* bloodstream infections (28 %) in ELBW infants (Wynn *et al.*, 2012).

A multidisciplinary approach to high-risk patients with accurate microbiological diagnosis, strict implementation of infection control measures and intensive care management of the septic infant all had a decisive effect on securing a successful outcome of *Cyberlindnera fabianii* infection in our patients. Future efforts should focus on the validation of risk factors identified in our NICU population and on the development of interventions for preventing a high incidence of *Cyberlindnera fabianii* infections.

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