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Original Article

# Investigation of a nosocomial outbreak of fungemia caused by *Candida pelliculosa* (*Pichia anomala*) in a Korean tertiary care center



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## KEYWORDS

*Candida pelliculosa*;  
Fungemia;  
Outbreak

**Abstract** *Background:* *Candida pelliculosa* is a rare pathogen of fungemia. There have been a few nosocomial outbreaks of *C. pelliculosa* fungemia in nurseries and pediatric intensive care units (ICU), hematologic units, and surgical ICU. We describe an epidemiologic outbreak investigation, including case findings of *C. pelliculosa* fungemia in South Korea.

*Methods:* This outbreak investigation conducted in a 940-bed, tertiary referral center, Ulsan, South Korea and included active microbial surveillance and a case–control study.

*Results:* A patient in the trauma intensive care unit (ICU) with multiple trauma developed *C. pelliculosa* fungemia, and 10 patients in the trauma ICU, medical ICU, and 2 general wards subsequently contracted *C. pelliculosa* fungemia during the next 24 days (November 16 and December 9, 2015). The 16s rRNA sequencing of 4 isolates showed that *C. pelliculosa* was verified with 99–100% similarity (GenBank accession number: KF317892.1), and these isolates were identical in the randomly amplified polymorphic DNA (RAPD) assay. A case–control study showed that medical staff and staying in the interventional radiology procedure room were risk factor for development of *C. pelliculosa* fungemia. After intervention including strict hand washing, disinfecting medical equipment, and contact precautions, there have been no new *C. pelliculosa* infections since December 10, 2015.

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**Conclusions:** This is the first report of a nosocomial outbreak involving 11 patients in 2 ICUs and 2 general wards caused by *C. pelliculosa* in South Korea. Infection control measures are important for decreasing transmission of *C. pelliculosa* in the hospital.

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## Introduction

*Candida pelliculosa*, also known as *Hansenula anomala* and *Pichia anomala*, is usually found in fruits, soil, and plants. It is a rare pathogen causing invasive infection.<sup>1</sup> Infection with *C. pelliculosa* was first reported in 1953, and it occurred in an infant who died of interstitial pneumonia.<sup>2</sup> Thereafter, there have been a few sporadic cases of *C. pelliculosa* infection, which have occurred mainly in infants, children, and immunocompromised patients.<sup>3–7</sup> In addition, there have been nosocomial outbreaks of *C. pelliculosa* fungemia in nurseries and pediatric intensive care units (ICU),<sup>8–13</sup> hematologic units,<sup>2</sup> and surgical ICUs.<sup>14</sup> Herein, we describe an epidemiologic outbreak investigation of 11 cases of fungemia caused by *C. pelliculosa* during 24 days in a single center in Ulsan, South Korea.

## Material and methods

### Hospital

Ulsan University Hospital is a 940-bed tertiary referral center located in Ulsan, South Korea. From November 16, 2015, to December 9, 2015 (a period of 24 days), there were 11 cases of *C. pelliculosa* fungemia (Fig. 1). Before this outbreak, no case of *C. pelliculosa* fungemia was noted at

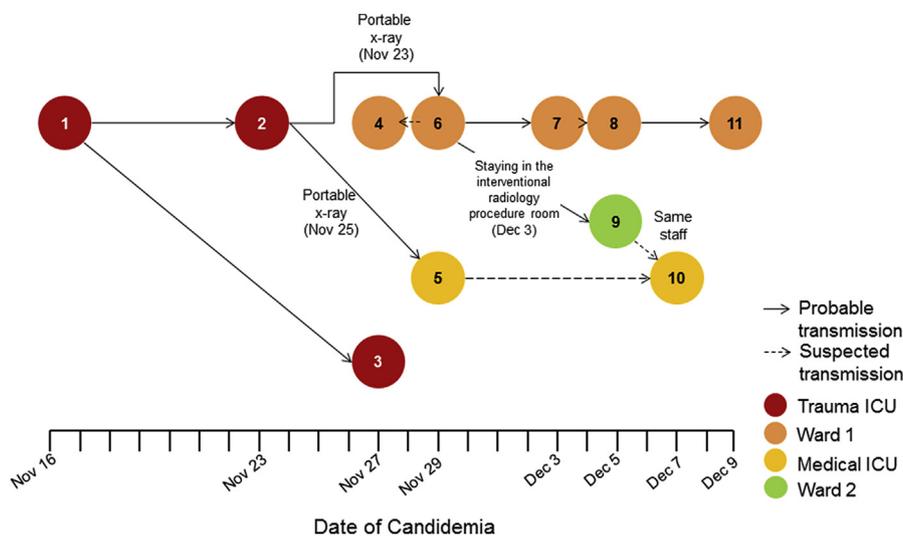
our hospital in 2015. In infection control office, we reviewed blood culture reports weekly for surveillance. At November 30, 2015, we noticed the cluster of *C. pelliculosa* fungemia, and started outbreak investigation.

### Study design

Cases were defined as those patients with a *C. pelliculosa* bloodstream infection. We retrospectively reviewed case patients' medical records regarding demographics, clinical characteristics, and treatment.

### Case–control study

We performed an unmatched case–control study to identify the risk factors for *C. pelliculosa* fungemia. We randomly selected three control patients without fungemia for each case-patients admitted to each wards (TCU, MICU, ward 1, and ward 2) for at least 48 h during the outbreak period (group 1 control-patients). In addition, we defined all patients who developed candidemia other than *C. pelliculosa* from September 1, 2015 to January 31, 2016 as group 2 control-patients. As there were only 2 patients with candidemia other than *C. pelliculosa* during the outbreak, we have broadened the period beyond the outbreak period to select the control patients.



**Figure 1.** Transmission map of outbreak of *Candida pelliculosa* fungemia. Three patients in trauma intensive care unit (ICU), 5 pediatric patients in ward 1, 2 patients in medical ICU, and 1 patient in ward 2 had *C. pelliculosa* fungemia. Spatiotemporally, portable x-ray machine, same staff and same ward may be associated with transmission in the different wards.

**Table 1** Clinical characteristics of patients with *Candida pelliculosa* fungemia.

No	Sex/age	Ward	Underlying disease	Onset of candidemia (hospital day)	Duration of candidemia	Previous or concomitant bacteremic infection	Previous antibiotic treatment	Central venous catheter	Catheter removal (days after onset of candidemia)	Catheter tip culture	Antifungal therapy	Outcome
1	F/76	TICU	Multiple trauma	2015/Nov/16 (19)	1	No	Yes	Yes	Yes (4)	No growth	Micafungin	Survived
2	F/50	TICU	Multiple trauma	2015/Nov/23 (22)	11	Yes	Yes	Yes	Yes (0)	No growth	Micafungin	Died (Candidemia related death)
3	M/47	TICU	Multiple trauma	2015/Nov/27 (17)	1	No	Yes	Yes	Yes (2)	No growth	Micafungin	Survived
4	M/6	Ward 1	Aplastic anemia, HCT recipient (4 months ago)	2015/Nov/27 (26)	4	No	No	Yes	Yes (5)	No growth	Caspofungin	Survived
5	M/52	MICU	Diabetes mellitus, chronic alcoholics, community-acquired pneumonia	2015/Nov/29 (7)	8	No	Yes	Yes	Yes (2)	No growth	Micafungin	Died (due to multi-drug resistant <i>A. baumannii</i> pneumonia)
6	F/18	Ward 1	Pituitary blastoma	2015/Nov/29 (38)	3	No	Yes	Yes	Yes (4)	No growth	Caspofungin	Survived
7	M/17	Ward 1	Acute lymphoblastic leukemia, s/p chemotherapy	2015/Dec/3 (10)	12	No	No	Yes	Yes (12)	Not done	Caspofungin	Survived
8	F/6	Ward 1	Colonic pseudoobstruction	2015/Dec/5 (9)	4	No	No	Yes	Yes (4)	Not done	Caspofungin	Survived
9	M/77	Ward 2	Renal pelvic cancer	2015/Dec/5 (10)	7	No	Yes	Yes	No	—	Fluconazole then micafungin	Died (Candidemia related death)
10	F/78	MICU	Large B cell neuroendocrine carcinoma	2015/Dec/7 (43)	8	No	Yes	Yes	No	—	Fluconazole then Micafungin	Died (Candidemia related death)
11	F/2	Ward 1	Myoneural disorder, seizure	2015/Dec/9 (18)	7	No	Yes	Yes	Yes (7)	No growth	Caspofungin	Survived

HCT, Hematopoietic cell transplantation; MICU, medical intensive care unit; TICU, trauma intensive care unit.

## Identification and antifungal susceptibility testing

All *C. pelliculosa* isolates were identified by VITEK II (BioMerieux, Lyon, France) and matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (BioMerieux, Lyon, France). The genomic DNA was extracted from the cultivated microorganism. The 16S rRNA gene was amplified with universal primers forward, 5'-AGTTT-GATCCTGGCTCAG-3'; reverse, 5'-GTATTGCCGCGGCTGCTG-3' and sequenced. Antifungal susceptibilities were determined using a VITEK II (BioMerieux, Lyon, France).

## Molecular investigation

### DNA extraction

The colonies were dispersed in 1 ml of PBS and centrifuged at 13,000 rpm for 2 min. Afterwards, the supernatant was removed. By adding 100  $\mu$ L 10% Chelex 100 resin (Bio-Rad Laboratories, Hercules, CA, USA) to the pellet, the mixture obtained was incubated at 56 °C for 15 min and boiled at 100 °C for 10 min. Finally, after centrifuging at 13,000 rpm for 2 min, the liquid left on the top was used for the randomly amplified polymorphic DNA (RAPD) assay.

### Randomly amplified polymorphic DNA (RAPD) assay

A total of 50  $\mu$ L RAPD mixture was prepared; 2  $\mu$ L of DNA, 2  $\mu$ L of 100 pmol M13 primary (5'-CAG GGT CCC GGT TCT-3'), 25  $\mu$ L of EconoTaq<sup>®</sup> PLUS GREEN 2X Master Mix (Lucigen, Middleton, WI, USA), and 21  $\mu$ L of distilled water. The amplification procedure implemented for the reaction mixture was as follows; 2 cycles, 5 min at 94 °C, 5 min at 40 °C, 5 min at 72 °C; and 40 cycles, 1 min at 94 °C, 1 min at 40 °C, and 2 min at 72 °C. PCR reaction was performed on a 2720 GeneAmp PCR system (Applied Biosystems, Foster City, CA, USA). PCR products were analyzed by gel electrophoresis on a 2% agarose gel.

## Statistical analysis

Categorical variables were compared using the  $\chi^2$  or Fisher's exact test, and continuous variables were compared using the Mann–Whitney *U* test, as appropriate. A *P* value <0.05 was considered statistically significant.

## Results

### Description of outbreak

The index patient was a 76-year-old female who was admitted to the trauma ICU (TICU) because of a pelvic bone fracture and crushing injury in a traffic accident on October 29, 2015. She underwent multiple surgeries and was treated with antibiotics (cefotaxime and vancomycin) for open wounds. She had a central venous catheter. On her 19th hospital day (November 16), her body temperature rose to 39 °C and blood culture yielded *C. pelliculosa* (1 of 2 sets). She was treated successfully with micafungin and discharged from the TICU on November 23. There were 2 subsequent cases of *C. pelliculosa* fungemia in the TICU 7 days and 9 days after the index date, respectively (Fig. 1).

Additionally, there was a subsequent outbreak involving 5 children in the ward 1 (No. 4, 6–8, 11) beginning on November 27 and 2 more patients (No. 5, 10) in the medical ICU beginning on November 29. An additional patient (No. 9) in ward 2 contracted *C. pelliculosa* fungemia on December 9. Spatiotemporally, the possible source of transmission from the case in the TICU (No. 2) to those in the medical ICU (No. 5) and ward 1 (No 6.) was the use of the same portable x-ray machine (Fig. 1). Patient No. 9 shared a room with patient No. 6 in the intervention center on December 3. Patient No. 10 possibly contracted *C. pelliculosa* fungemia from patient No. 5 (same ward) or from patient No. 9 (same staff).

## Characteristics of patients

The age of the patients ranged from 2 to 78 years, and 6/11 (55%) were women (Table 1). Except for 2 patients with candidemia lasting for only 1 day, most had persistent candidemia with duration ranging from 3 to 12 days. Eight had previously received antibiotics. All had central venous catheters, and 9 underwent removal of the central venous catheter. Central line tip cultures of 7 patients were sent to the clinical microbiology laboratory, and all obtained results were negative. All patients were treated with echinocandin, and 7 survived (crude mortality 36.3%).

## Case–control study

Table 2 shows the comparison of the characteristics of patients with *C. pelliculosa* fungemia with those of patients without fungemia during outbreak (control group 1) and those of patients with candidemia other than *C. pelliculosa* (control group 2). There were 14 patients with candidemia other than *C. pelliculosa* from September 2015 to January 2016. As shown in Table 2, when compared to group 1, a pediatric hematologist more often cared patients with *C. pelliculosa* fungemia (*P* = 0.01), and other staffs less often cared patients with *C. pelliculosa* fungemia (*P* = 0.001). Patients with *C. pelliculosa* more commonly had the central venous catheter (*P* < 0.001), treated with mechanical ventilation (*P* = 0.03) and total parenteral nutrition (*P* = 0.003). Also, they more frequently visited to the interventional radiology procedure room during outbreak period than control group 1 patients (*P* = 0.06). Although we suspected that use of portable x-ray machine A may be responsible for transmission of *C. pelliculosa*, there was no statistical difference between case and control group (*P* = 0.49).

There were no differences between patients with *C. pelliculosa* and those with other candidemia regarding dwelling of central venous catheter (*P* = 0.11), being treated with mechanical ventilation (*P* > 0.99) and receipt of total parenteral nutrition (*P* = 0.11). At ward 1, *C. pelliculosa* fungemia were more commonly developed than other candidemia (*P* = 0.06).

## Intervention for infection control

After detection of the outbreak, we began the intervention including hand-hygiene education, isolation of all patients

**Table 2** Comparison of the characteristics of patients with *C. pelliculosa* fungemia with those of patients without fungemia during outbreak (control group 1) and those of patients with candidemia other than *C. pelliculosa* (control group 2).

	Case (n = 11)	Control group 1 (n = 33)	P value <sup>a</sup>	Control group 2 (n = 14)	P value <sup>b</sup>
Age, median (IQR)	47 (6–76)	20 (2–65)	0.25	73 (42–78)	0.08
Male, n (%)	5 (46)	20 (61)	0.49	10 (71)	0.24
<b>Ward, n (%)</b>					
TCU	3 (27)	9 (27)	>0.99	1 (7)	0.29
MICU	2 (18)	6 (18)	>0.99	4 (29)	0.66
Ward 1	5 (46)	15 (46)	>0.99	1 (7)	0.06
Ward 2	1 (9)	3 (9)	>0.99	2 (14)	>0.99
Other	0 (0)	0 (0)	N/A	6 (43)	0.02
<b>Attending staff</b>					
Trauma team	3 (27)	7 (21)	0.70	1 (7)	0.29
Pediatric hematologist	3 (27)	0 (0)	0.01	1 (7)	0.29
Pediatrician A	2 (18)	1 (3)	0.15	0 (0)	0.18
Oncologist A	2 (18)	2 (6)	0.27	0 (0)	0.18
Others	1 (9)	23 (70)	0.001	12 (86)	<0.001
Central venous catheter, n (%)	11 (100)	8 (24)	<0.001	10 (71)	0.11
Mechanical ventilation, n (%)	5 (46)	4 (12)	0.03	6 (43)	>0.99
Urinary catheter, n (%)	8 (73)	15 (46)	0.12	8 (57)	0.68
Arterial catheter, n (%)	5 (46)	7 (21)	0.14	6 (43)	>0.99
Major surgery, n (%)	3 (27)	4 (12)	0.34	4 (29)	>0.99
Total parenteral nutrition, n (%)	8 (73)	7 (21)	0.003	5 (36)	0.11
Use of H2 blocker, n (%)	7 (64)	24 (73)	0.71	6 (43)	0.30
Use of proton pump inhibitor, n (%)	2 (18)	1 (3)	0.15	3 (21)	>0.99
Use of corticosteroid, n (%)	2 (18)	14 (42)	0.28	2 (14)	>0.99
Previous or concomitant bacteremia, n (%)	1 (9)	1 (3)	0.44	2 (14)	>0.99
Use of broad spectrum antibiotics, n (%)	8 (73)	12 (36)	0.08	11 (79)	>0.99
Use of portable x-ray machine A during outbreak, n (%)	7 (64)	15 (46)	0.49	0 (0)	<0.001
Visit to intervention center during outbreak, n (%)	2 (18)	0 (0)	0.06	0 (0)	0.18
In-hospital mortality, n (%)	4 (36)	4 (12)	0.09	8 (57)	0.30
Length of hospital stay (days), median (IQR)	66 (27–75)	15 (7–45)	0.004	28 (16–34)	0.03

<sup>a</sup> Compared between case and control group 1.

<sup>b</sup> Compared between case and control group 2.

IQR, interquartile range; MICU, medical intensive care unit; TCU, trauma intensive care unit.

with *C. pelliculosa* fungemia in single room. Aprons and gloves were worn for contact. With suspicion of the use of the identical x-ray machine as a probable source of transmission of *C. pelliculosa*, we disinfected the x-ray cassettes using alcohol and quaternary ammonium compounds. There have been no new cases of *C. pelliculosa* infection since December 10, 2015 (Fig. 2).

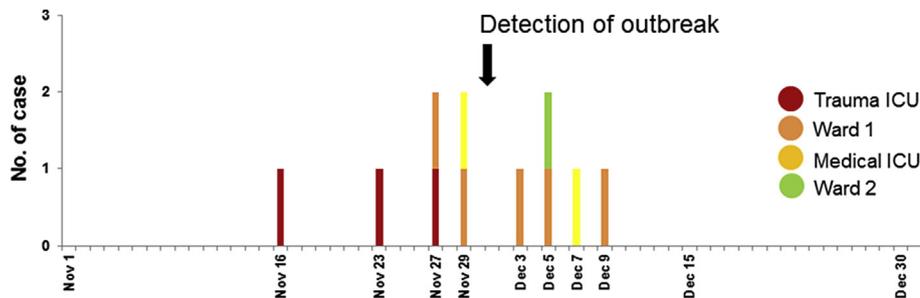
### Antifungal susceptibility testing

Table 3 shows antifungal susceptibility test results of 30 isolates from 11 patients. The antifungal susceptibility pattern was almost identical between the 30 isolates, except for 2 isolates showing a minimal inhibitory

concentration (MIC) for amphotericin B of 0.5 mg/L and other 2 isolates showing an MIC for fluconazole of less than 1 mg/L (Table 3). Overall, all isolates were susceptible to amphotericin B, fluconazole, voriconazole, caspofungin, and micafungin.

### Molecular studies

We performed 16s rRNA sequencing and RAPD assay for 4 isolates from 3 cases in the ward 1 (No. 7, 8, 11) and 1 case (No. 10) in the medical ICU. As stored *C. pelliculosa* isolates were contaminated, we could not perform 16s rRNA sequencing and RAPD assay for the other isolates. The 16s rRNA sequencing showed that *C. pelliculosa* was verified



**Figure 2.** Epidemiologic plot of *Candida pelliculosa* fungemia. From November 16, 2015 to December 9, 2015, there were 11 cases of *C. pelliculosa* fungemia. We noticed the cluster of *C. pelliculosa* fungemia at November 30, 2015, and started outbreak investigation.

**Table 3** Result of antifungal susceptibility testing of 30 *Candida pelliculosa* isolates from 11 patients.

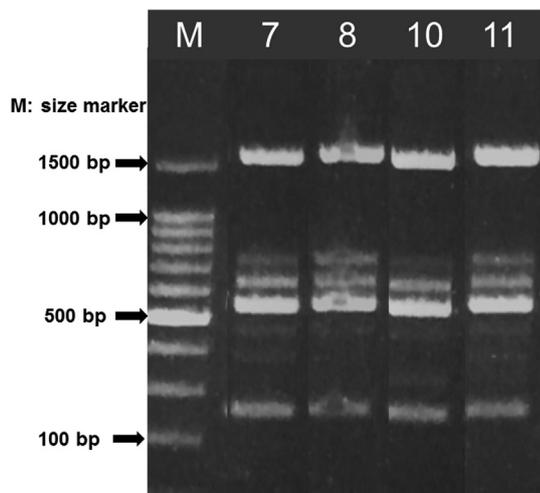
Antifungal agents	Minimal inhibitory concentrations (MICs, mg/L), (No. of isolates)
Amphotericin B	≤0.25 (28), 0.5 (2)
Fluconazole	≤1 (2), 2 (28)
Voriconazole	≤0.12 (30)
Caspofungin	≤0.25 (30)
Micafungin	≤0.06 (30)

with 99–100% similarity (GenBank accession number: KF317892.1), and these 4 outbreak isolates were identical in the RAPD assay (Fig. 3).

**Discussion**

To the best of our knowledge, there have been 8 studies describing outbreaks of *C. pelliculosa* infection

(Table 4)<sup>2,8–14</sup>; of these, 4 were from Brazil,<sup>2,8,10,13</sup> and the remaining 4 were from the United Kingdom,<sup>12</sup> India,<sup>9</sup> Taiwan,<sup>11</sup> and Croatia,<sup>14</sup> respectively. Of these 8 reports, 6 occurred in neonatal or pediatric patients,<sup>8–13</sup> and the other 2 occurred in adult patients in hematologic units<sup>2</sup> and a surgical ICU.<sup>14</sup> Herein, we describe the first nosocomial outbreak of *C. pelliculosa* fungemia in South Korea. It began in an adult patient with a crushing injury and then subsequently involved 5 pediatric and 5 adult patients in different wards. We initially considered sharing an x-ray cassette, the bed at the angioplasty center, and the hands of the medical staff as possible sources of transmission by spatiotemporal relationship (Fig. 1). To identify risk factors for *C. pelliculosa* fungemia, we performed a case–control study which showed that dwelling of central venous catheter, receipt of total parenteral nutrition, being treated with mechanical ventilation, one medical staff (pediatric hematologist) and staying in the interventional radiology procedure room were associated with development of *C. pelliculosa* fungemia. Previous studies evaluating *C. pelliculosa* outbreaks demonstrated that presence of central venous catheters, previous antibiotic use, and other invasive procedures were associated with development of *C. pelliculosa* fungemia (Table 4).<sup>8,13</sup> However, factors including dwelling of central venous catheter, receipt of total parenteral nutrition, and being treated with mechanical ventilation are known factors of development of candidemia<sup>15</sup> and there were no differences between patients with *C. pelliculosa* and those with other candidemia in this study. We believe that visiting to the intervention center during outbreak and a pediatric hematologist were probable risk factors for development *C. pelliculosa* fungemia. Since *C. pelliculosa* is environmental yeast,<sup>9</sup> it is plausible that the outbreak was induced by the hands of medical staff or medical equipment, and Chakrabarti et al. identified medical staff colonizing with *C. pelliculosa*.<sup>9</sup> Although we fail to demonstrate the use of portable x-ray machine was associated with transmission of *C. pelliculosa* by case–control study, there was no link between patient 2 at TCU and patient 6 at ward 1 nor patient 5 at MICU, it may be associated with transmission of *C. pelliculosa* between the different wards. Taken together, patients who had been received total parenteral nutrition and had central venous catheters may have colonized to *C. pelliculosa* by the hands of the medical staff or medical equipment and then



**Figure 3.** Agarose gel electrophoresis of polymerase chain reaction (PCR) products of 4 *Candida* isolates with species-specific primer for *Candida pelliculosa*. Lane M indicates molecular weight size reference marker (100-bp ladder), randomly amplified polymorphic DNA (RAPD) patterns of isolates from patient 7, 8, 10, 11 were identical to each other.

**Table 4** Published reports of outbreak of fungemia caused by *Candida pelliculosa*.

Reference/Year of publication	Nation	Number of patients with <i>C. pelliculosa</i> fungemia	Duration of outbreak	Patient population or hospital services	Risk factors for <i>Candida pelliculosa</i> infection analyzed by case control study	Mortality
Murphy et al. 1986 <sup>12</sup>	UK	52	13 months	Neonates	(–)	–
Thuler et al. 1997 <sup>2</sup>	Brazil	24	3 months	Hematologic units	(–)	0%
Chakrabarti et al. 2001 <sup>9</sup>	India	379	23 months	Neonates, children	Lower gestational age, low birth weight, longer duration of hospital stay	42.4%
Kalenic et al. 2001 <sup>14</sup>	Croatia	8	4 months	Adults in surgical ICU	Duration of blood alkalosis	38%
Aragao et al. 2001 <sup>8</sup>	Brazil	4	2 months	Neonates in nursery	CVC, TPN, previous antibiotic use, other invasive procedure	0%
Pasqualotto et al. 2005 <sup>13</sup>	Brazil	17	16 months	Children in pediatric ICU	CVC catheter	41.2%
da Silva et al. 2013 <sup>10</sup>	Brazil	5	4 months	Neonates	(–)	0%
Lin et al. 2013 <sup>11</sup>	Taiwan	6	1 month	Infants	(–)	16.7%
Ours	South Korea	11	24 days	Adult, pediatric patients at TICU, MICU, and 2 general wards	(–)	36.3%

ICU, intensive care unit; CVC, central venous catheter; TPN, total parenteral nutrition; TICU, trauma intensive care unit; MICU, medical intensive care unit.

subsequently developed *C. pelliculosa* fungemia. Our investigation adds the possibility of a nosocomial outbreak of *C. pelliculosa* fungemia not only in pediatric patients but also in adults through the hands of the medical staff or an environmental source.

An antifungal susceptibility test showed the MIC of fluconazole, amphotericin B, voriconazole, caspofungin, and micafungin being within the susceptible range. Most patients had been treated with amphotericin B or fluconazole.<sup>2,5,9–11,13,14</sup> We used echinocandin as the primary therapy for candidemia.<sup>16</sup> Although there is limited data, a previous study showed that echinocandin had good antifungal activity.<sup>17,18</sup> As the crude mortality in our study was within the range reported previously (0–42.4%), and 2 of 3 patients (No. 9, 10) who died related to candidemia had a retained central venous catheter, our data suggests that echinocandin may be a good option for treatment of *C. pelliculosa* infection.

Compared to previous reports, the duration of our outbreak was brief with efforts to block transmission of *C. pelliculosa* including thorough hand washing, contact precautions, and cleansing medical equipment (Table 4). Although previous studies used prophylactic antifungal agents to control outbreaks,<sup>2,11</sup> our outbreak was terminated without the use of prophylactic antifungal agents for other patients. We believe that the reinforcement of infection control is most important factor for management of outbreaks caused by *C. pelliculosa*.

There are several limitations to note. First, we did not perform environmental sampling or hand culture surveys. Therefore, the source of transmission cannot be determined. However, previous outbreak investigations had failed to identify the source of the transmission.<sup>2,8,13,14</sup> To overcome of this limitation, we have performed case–control study which indicated that medical staff, and

medical environment may be associated with transmission of *C. pelliculosa*. Second, we performed the RAPD assay and 16s rRNA sequencing only for isolates from 4 patients, because the other isolates were contaminated and were thus unavailable for molecular analysis. However, we believe that this outbreak was caused by a single strain because no cases of *C. pelliculosa* infection were noted before or after this outbreak, antifungal susceptibility tests were almost identical between the isolates, and there were epidemiologic links.

In conclusion, clinicians should be aware of the possibility of an outbreak when an unusual pathogen like *C. pelliculosa* is isolated. Strict hand washing regimen and reinforcement of infection control is important for control of the outbreak.

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None reported.

## Conflict of interest

There are no potential conflicts of interest for any authors.

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