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Persistent vs non-persistent candidaemia in adult patients in 2007-2016: A retrospective cohort study

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Summary

Objectives: Persistent candidaemia (PC) is a recognised complication of candidaemia. Our objective was to evaluate risk factors and clinical significance of PC in adult patients.

Methods: This is a retrospective, cohort study. We compared PC with non-PC. All patients with blood cultures positive for *Candida* species were identified from a microbiological database in the hospital district of Helsinki and Uusimaa from 2007 to 2016. PC was defined as an isolation of the same *Candida* species from positive blood culture for ≥5 days.

Results: PC criteria were fulfilled by 75/350 patients (21.4%). No significant difference emerged between persistent and non-persistent cases caused by non-albicans *Candida* species (37.3% vs 35.1%, $P = .742$). The length of hospital stay before onset of candidaemia was longer before PC (hospital stay > 7 days; 73.3% vs 59.6%, $P = .043$). No significant impact on 30-day mortality was observed (20.0% vs 15.5%, $P = .422$). Using multivariable regression analysis, we found the presence of central venous catheter (CVC) (OR = 2.71, 95% CI 1.31-5.59), metastatic infection foci (OR 3.60, 95% CI 1.66-7.79) and ineffective empirical treatment (OR = 3.31, 95% CI 1.43-7.65) to be independent risk factors for PC. In subgroup analysis, early source control was identified as a protective factor against PC (30.5% vs 57.7%, $P = .002$).

Conclusion: The presence of CVC, metastatic infection foci and ineffective empirical treatment were independently associated with PC in adult patients. Active search for and treatment of metastatic infection foci and removal of CVC are key elements for preventing PC.

KEYWORDS
adult patients, central venous catheter, metastatic infection foci, Persistent candidaemia

1 | INTRODUCTION

Candida is a major cause of nosocomial infections,[1] and candidaemia causes significant mortality ranging between 30% and 45%.[2-5] Furthermore, candidaemia generates significant healthcare costs.[2] Its main complications include metastatic infection foci and death.[6]

Persistent candidaemia (PC) is frequently recognised as another complication of candidaemia. Underlying factors that can influence the persistence of blood culture positivity in candidaemia

include the host's baseline characteristics (eg cancer, immunosuppressive medication, neutropenia), antifungal resistance, efficacy of therapeutic management and source control. However, the literature on PC is scarce. The most relevant problem in evaluating PC is the lack of a homogeneous definition of PC.[7] Most studies evaluating PC include adult and child populations or have been conducted only in neonatal populations.[2,8-11] This complicates any generalisation of the results to adult patients. The definition of PC ranges from >1 day to 7 days in literature, which influences PC incidence rates.[7] The reported incidence rates of PC vary from 8% to 93%.[7] However, the reported rates are at 11%-37% when considering only studies with a definition of candidaemia duration of 3-5 days.[12-15] Although several studies have evaluated PC, the data are mostly from research designed to consider other elements than PC.[16-18]

The aim of this study was to evaluate the underlying risk factors and clinical significance of PC, defined as blood culture positivity persisting for 5 days or longer. We compared adult patients with PC with non-persistent cases in a retrospective analysis from Southern Finland during 2007-2016.

2 | PATIENTS AND METHODS

2.1 | Study design

An observational, retrospective cohort study including adult patients with candidaemia was conducted in the hospital district of Helsinki and Uusimaa (population 1.6 million) in Finland from January 2007 to December 2016. All patients with blood cultures positive for *Candida* species were identified from the laboratory database. Patients aged under 18 years were excluded. The clinical data were collected from the cases treated in secondary and tertiary care hospitals. Patient demographics and medical history, including age, sex, admitted ward, underlying diseases, a primary source of infection, risk factors for candidaemia, catheter removal, *Candida* species, laboratory findings, details of antimicrobial susceptibility results and antimicrobial therapy, were reviewed. The persistent and non-persistent candidaemia cases were identified and compared to evaluate the underlying causes and clinical significance of PC. Complications and 30-day overall mortality were assessed.

Details of microbiological identification and susceptibility testing are presented in an earlier publication of this study.[19] As earlier has been described, identification of *Candida* isolates was based on traditional methods using morphological and biochemical features (ID 32 C®, bioMérieux) before 2012. Since 2012, the strains have been mainly identified by MALDI-TOF technology (Vitek MS, bioMérieux) and by sequencing of the ITS gene,[20] if necessary. Susceptibility testing was performed using agar diffusion method (Etest®, bioMérieux) according to the manufacturer's instructions. The results were interpreted by using the CLSI breakpoints until the end of 2010. Interpretation has been conducted according to the EUCAST clinical breakpoint since the beginning of 2011. The susceptibility testing for anidulafungin started routinely in 2011, and earlier it was performed on demand.

The authors confirm adherence to the ethical policies of the journal. The study protocol was approved by the review board of the Inflammation Center at Helsinki University Hospital. No informed consent was needed because of the retrospective nature of the study.

2.2 | Definitions

An episode of candidaemia was defined as at least one blood culture positive for *Candida* species. If the patient had more than one episode of candidaemia, only the first episode was included in the study. Recurrent episodes were excluded (n = 24). PC was defined as an isolation of the same *Candida* species from any positive blood culture taken ≥5 days after the first positive blood samples were drawn. Non-PC was defined as all other candidaemia cases than persistent ones with negative blood cultures taken at least once. Patients were excluded if death occurred <5 days after the onset of candidaemia (n = 7), if no antifungal treatment was provided(n = 6), or if no negative blood cultures were drawn (n = 90). Patient records were evaluated from tertiary and secondary care hospitals. Twenty-one cases were treated in primary care hospitals, and the medical records were incomplete. These patients were excluded. Metastatic complications were considered endophthalmitis or chorioretinitis, endocarditis or pericarditis, vascular complications, and dissemination to other solid organs. Source control and its timing were assessed, including abscess drainage, catheter removal, resolution of urinary tract obstruction or treatment for gastrointestinal perforation. Source control was regarded as early when performed within 48 hours after onset of candidaemia. Empirical antifungal treatment was defined as treatment started on clinical suspicion of candidaemia before confirmation of candidaemia diagnosis. Antifungal treatment was considered ineffective if the *Candida* species isolated from blood cultures was resistant to the initially administered antifungal agent.

Neutropenia was specified as a neutrophil count of less than 0.5 x 10^9/L occurring within the last two weeks before the onset of candidaemia. Comorbidities were evaluated using the McCabe classification.[21] It classifies the severity of underlying illnesses with a score 1-3, where 1 indicates non-fatal prognosis (≥5 years), 2 indicates an ultimately fatal prognosis (in 1-4 years) and 3 represents a rapidly fatal prognosis (within 1 year). Prior corticosteroid treatment was defined as a use of prednisolone dose ≥ 15 mg/d for more than 3 weeks. Adherence to the guidelines of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the Infectious Diseases Society of America (IDSA) was evaluated using the EQUAL Candida Score of the European Confederation of Medical Mycology (ECMM).[22] The maximum score was 22 points for patients with a central venous catheter (CVC) and 19 for those without a CVC.

2.3 | Statistical analysis

Categorical variables were summarised as counts and percentages and compared using the chi-square or Fisher's exact test, as appropriate. Continuous variables with a non-normal distribution were described as median and interquartile range (IQR) and compared using the Mann-Whitney U test. *P*-values ≤ .05 were considered to indicate statistical significance. Odds ratios (ORs) were calculated with 95% confidence interval (CI). Risk factors associated with PC were computed in a multivariable logistic regression analysis. The regression analysis included variables having univariate *P*-value < .1 and was not multicollinear. SPSS version 25 (SPSS Inc) was used for all analyses.

3 | RESULTS

We identified a total of 374 episodes of candidaemia in 350 adult patients in our hospital district during the study period. The definition of PC was fulfilled by 75/350 cases (21.4%), while 151/350 cases (43.1%) were considered non-persistent.

The median duration of blood culture positivity in PC was 9.0 days (IQR 7.0-15.0). The median number of follow-up blood cultures was 5.0 (IQR 3.0-8.0, range 2-44) per patient. In many of the cases, control blood cultures were taken every other or every third day, but the follow-up blood cultures were taken daily for only 9.7% of the patients (22/226). Species distributions and susceptibility results are shown in Table 1. Non-albicans *Candida* spp. caused 37.3% of PC and 35.1% of non-persistent cases without a significant difference (*P* = .742). However, candidaemia caused by *C dubliniensis* was more common among non-persistent than PC cases (PC 1.3% vs non-PC 7.9%), but the difference did not reach statistical significance (*P* = .065). *C albicans* was the leading cause (62.7%) of PC, followed by *C glabrata* (17.3%) and *C parapsilosis* (5.3%). Resistance rate for fluconazole was overall 21.3% for PC and 13.9% for non-persistent cases (Table 1). Fluconazole resistance was rare (2.2%) for *Candida* spp. other than *C glabrata*, but the rate was high among PC (76.9%) and non-persistent cases (80.0%) caused by *C glabrata*. Anidulafungin susceptibility testing has been performed routinely since 2011 in our hospital district and earlier for only selected cases. Resistance to anidulafungin was rare, seen in only 4/168 cases (2.4%). Amphotericin B resistance was also rare; a total of 2/225 cases (0.9%) were resistant to amphotericin B.

The baseline characteristics of PC vs non-persistent cases are displayed in Table 2. The median age for persistent cases was 61.0 years (IQR 50.0-70.0) and for non-persistent cases 62.0 years (IQR 48.0-73.0). Among persistent cases, 57.3% were male, as were 64.2% of non-persistent cases. No significant difference between the two groups emerged regarding age, gender, comorbidities or prior drug exposures. However, previous use of fluconazole

TABLE 1 *Candida* bloodstream isolates in persistent vs non-persistent candidaemia

	Persistent n (%), n = 75	Non-persistent n (%), n = 151	*P*
Albicans vs non-albicans *Candida* spp.			.742
C albicans	47/75 (62.7)	98/151 (64.9)	
Non-albicans	28/75 (37.3)	53/151 (35.1)	
Candida species			.232
C albicans	47 (62.7)	98 (64.9)	
C glabrata	13 (17.3)	20 (13.2)	.418
C parapsilosis	4 (5.3)	5 (3.3)	
C tropicalis	3 (4.0)	3 (2.0)	
C krusei	3 (4.0)	1 (0.7)	
C dubliniensis	1 (1.3)	12 (7.9)	.065
Others or multiple	4 (5.3)	12 (7.9)	
Fluconazole resistance rate			
All	16/75 (21.3)	21/151 (13.9)	
C albicans	1/47 (2.1)	1/98 (1.0)	
C glabrata	10/13 (76.9)	16/20 (80.0)	
C parapsilosis	1/ 4 (25.0)	1/ 5 (20.0)	
C tropicalis	0/3	0/3	
Anidulafungin resistance rate	2/56 (3.6)	2/112 (1.8)	
C albicans	0/33	0/70	
C glabrata	0/10	1/17 (5.9)	

Abbreviation: Spp, species

TABLE 2 Baseline characteristics of persistent vs non-persistent candidaemia

	Persistent	Non-persistent	
	n (%)	n (%)	
	n = 75	n = 151	*p*
Male	43 (57.3)	97 (64.2)	.314
Age (median, IQR)	61.0 (50.0-70.0)	62.0 (48.0-73.0)	.424
Department at onset of candidaemia			
ICU	12 (16.0)	16 (10.6)	1
Surgical	37 (49.3)	64 (42.4)	.549
Medical	12 (16.0)	41 (27.2)	.062
Haematology-oncology	5 (6.7)	8 (5.3)	.790
Others	9 (12.0)	22 (14.6)	.270
ICU			
ICU at onset of candidaemia	12 (16.0)	16 (10.6)	.246
Admission to ICU after onset of candidaemia	7 (9.3)	14 (9.3)	.988
ICU before candidaemia diagnosis within 30 d	24 (32.0)	35 (23.2)	.155
Comorbidities			
McCabe			
1	20 (26.7)	53 (35.1)	1
2	40 (53.3)	68 (45.0)	.178
3	15 (20.0)	30 (19.9)	.493
Diabetes mellitus			
Malignancy	18 (24.0)	34 (22.5)	.867
Solid organ tumour	17 (22.7)	28 (18.5)	.465
Haematological malignancy	6 (8.0)	15 (9.9)	.639
Predisposing factors			
Dialysis	10 (13.3)	11 (7.3)	.140
Intravenous drug abuse	6 (8.0)	21 (13.9)	.276
Prior GI surgery	24 (32.0)	28 (18.5)	.024
Neutropenia	5 (6.7)	11 (7.3)	.865
Chemotherapy	6 (8.0)	11 (7.3)	.848
Solid organ transplantation	2 (2.7)	3 (2.0)	1.000
Hematopoietic stem cell transplantation	2 (2.7)	7 (4.6)	.721
Concomitant bacteremia within ±3 d	10 (13.3)	23 (15.2)	.704
Prior drug exposure			
Antibiotics[a]	39 (35.1)	72 (47.7)	.541
Fluconazole[b]	18/74 (24.3)	24 (15.9)	.140
Corticosteroids	6 (8.0)	11 (7.3)	.848
Other immunosuppressive medication	4 (5.3)	10 (6.6)	.705
Length of hospital stay prior to candidaemia			
0-7 d	20 (26.7)	61 (40.4)	
>7 d	55 (73.3)	90 (59.6)	.043

Abbreviations: GI, gastrointestinal; ICU, intensive care unit; IQR, interquartile range.

[a]Broad-spectrum antibiotics with anaerobic coverage.

[b]Data are missing for one PC case.

was slightly more frequent before diagnosis for PC than before non-PC diagnosis (24.0% vs 15.9%, respectively, P = .140). Persistent cases were diagnosed less at medical departments (16.0% vs 27.2%, P = .062), with half of the cases diagnosed at surgical departments. The association of prior gastrointestinal (GI) surgery with PC was significant (32.0% vs 18.5%, P = .024) in

univariate analysis. Length of hospital stay before onset of PC as opposed to non-PC was longer (hospital stay > 7 days; PC 73.3% vs non-PC 59.6%, *P* = .043).

Therapeutic management and clinical outcome are shown in Table 3. Fluconazole was the most common initial antifungal agent for both PC and non-PC (54.1% vs 62.9%, *P* = .202). Overall, an effective antifungal therapy was started empirically for 15.9% (36/226) of all patients without a significant difference between the groups (17.3% vs 15.2%, *P* = .329). However, an ineffective antifungal agent was started empirically more often for persistent than non-persistent cases (22.7% vs 10.6%, *P* = .011). The median duration of an ineffective treatment after the first positive blood culture was drawn was 2.5 days (IQR 1.75-4.5, range 1-6 days) for PC and 1.9 days (IQR 1.0-2.0, range 1-7 days) for non-PC.

The presence of CVC (68.0% vs 46.4%, *P* = .002) and catheter-related infection (42.7% vs 19.2%, *P* = .003) were more common in PC than in non-PC. A significant association was observed with metastatic infection foci between persistent and non-persistent cases (29.3% vs 13.2%, *P* = .003). Patients with PC had more ocular candidiasis (9.3% vs 2.6%, *P* = .045), other solid organ complications (18.7% vs 8.6%, *P* = .028) and vascular complications (6.7% vs 0.7%,*P* = .016) than non-persistent cases. Vascular complications (n = 6) included infected thromboses or thrombophlebitis (4/6, 66.7%) and infection of intravascular prostheses (2/6, 33.3%). Other solid organ complications (n = 27) comprised abscesses (6/27, 22.2%), pulmonary lesions (10/27, 37.0%), infection of prosthetic devices (3/27, 11.1%), osteomyelitis (2/27, 7.4%) and dissemination to several organs (6/27, 22.2%). During the 10-year study period, the overall 30-day mortality of candidaemia in the hospital district of Helsinki and Uusimaa was 31%. The 30-day mortality rate was 20.0% for PC and 13.9% for non-PC (*P* = .239).

The EQUAL Candida Score was calculated to analyse adherence to guidelines. The median EQUAL Candida Score was 13.0 (IQR 11.0-15.0, range 8-21). The median score for patients with CVC was 14.0 (IQR 11.0-16.0, range 8-21) and for patients without CVC 11.0 (IQR 11.0-14.0, range 8-18). Echocardiography was performed for 53.1% (120/226) and ophthalmoscopy for only 23.5% (53/226) of patients. Follow-up blood cultures were taken daily only for 9.7% (22/226) of the patients. Adherence was higher in patients who survived 30 days after onset of candidaemia than in non-survivors (*P* = .004).

TABLE 3 Therapeutic management and outcome of persistent vs non-persistent candidaemia

	Persistent n (%), n = 75	Non-persistent n (%), n = 151	*P*
Initial antifungal therapy			
Fluconazole	40 (54.1)	95 (62.9)	.202
Echinocandin	33 (44.6)	53 (35.1)	.169
Other or combination	1 (1.4)	3 (2.0)	
Empirical antifungal therapy			
AF started after blood culture result available	36 (48.0)	94 (62.3)	1
Effective AF started empirically	13 (17.3)	23 (15.2)	.329
AF empirically with suboptimal dose	9 (12.0)	18 (11.9)	.556
Ineffective empirical AF	17 (22.7)	16 (10.6)	.011
Source of infection			
Primary	5 (6.7)	23 (15.2)	1
Catheter-related	32 (42.7)	29 (19.2)	.003
GI	22 (29.3)	43 (28.5)	.126
Urinary	5 (6.7)	27 (17.9)	.817
Other	11 (14.7)	29 (19.2)	.359
Source control			
Source control during infection within applicable cases	52/59 (88.1)	75/78 (96.2)	.100
Early source control (<48 h) within applicable cases	18/59 (30.5)	45 /78 (57.7)	.002
Central venous catheter	51 (68.0)	70 (46.4)	.002
Early removal of CVC (<48 h) in applicable cases	24/51 (47.1)	32/70 (45.7)	.884
Patients with metastatic infection foci	22 (29.3)	20 (13.2)	.003
Endophthalmitis or retinitis	7 (9.3)	4 (2.6)	.045
Endocarditis or pericarditis	3 (4.0)	3 (2.0)	.401
Vascular complication	5 (6.7)	1 (0.7)	.016
Other solid organ complication	14 (18.7)	13 (8.6)	.028
30-d mortality	15 (20.0)	21 (13.9)	.239

Abbreviations: AF, antifungal; CVC, central venous catheter; GI, gastrointestinal.

TABLE 4 Multivariable regression analysis for independent risk factors of persistent candidaemia

	Univariate OR	95% CI	*P*	Multivariable OR	95% CI	*P*
Medical department during candidaemia diagnosis	0.51	0.25-1.04	.065	0.54	0.24-1.17	.118
CVC	2.46	1.38-4.40	.002	2.71	1.31-5.59	.007
Prior GI surgery	2.07	1.10-3.90	.025	1.28	0.61-2.68	.521
Metastatic infection foci	2.72	1.37-5.39	.004	3.60	1.66-7.79	.001
C dubliniensis	0.16	0.02-1.23	.078	0.21	0.03-1.70	.143
Ineffective empirical treatment	2.47	1.17-5.23	.018	3.31	1.43-7.65	.005
Hospital stay > 7 d before candidaemia diagnosis	1.86	1.02-3.42	.044	1.37	0.67-2.80	.392

Abbreviations: CI, confidence interval; CVC, central venous catheter; GI, gastrointestinal; OR, odds ratio.

However, no significant difference in guideline adherence was present between PC and non-PC cases (median score for PC 13.0 vs for non-PC 12.0, *P* = .068).

Using multivariable regression analysis (Table 4), we found the presence of CVC (OR = 2.71; 95% CI 1.31-5.59), metastatic infection foci (OR = 3.60; 95% CI 1.66-7.79) and ineffective empirical treatment (OR = 3.31; 95% CI 1.43-7.65) to be independent risk factors for PC. An applicable source of infection for source control was identified for 59 PC cases and for 78 non-PC cases (Table 3). In subgroup analysis, an early source control (within <48 hours of candidaemia onset) was more common in non-PC (PC 30.5% vs non-PC 57.7%, *P* = .002).

4 | DISCUSSION

We investigated the risk factors and clinical significance of PC in adult patients during a 10-year study period. Persistent candidaemia was found in 75 cases during the study period. Factors independently associated with PC were the presence of CVC at the onset of candidaemia, metastatic infection foci and ineffective empirical antifungal treatment. Catheter-related infection was the most common source of infection in persistent cases. CVC has been demonstrated as a risk factor for PC in other studies as well.[11,23-25] However, a recent cohort study conducted in adult patients did not find a significant association between CVC andPC.[12] In their study, CVC was a very common finding overall in both PC and non-PC groups (80% vs 72%), but the difference did not reach statistical significance.

The presence of CVC is a prominent risk factor for PC; however, the timing of CVC removal is complex. The association between early removal of CVC and PC was not significant in our study, supported by another recent study.[24] Nucci et al[26] showed that early CVC removal had no effect on persistent or recurrent candidaemia or time to mycological eradication, although earlier studies have reported an association of improved outcome and faster mycological eradication with prompt CVC removal.[27,28]

Metastatic infection foci were more prominent in PC than in non-PC cases. Similarly, unexpected additional infection sites were associated with PC also in an earlier analysis.[12] This supports the assumption that an active search for metastatic infection foci is crucial during the treatment of PC. Early source control was a protective factor against PC in a subgroup analysis in our study.

Fluconazole resistance among *C glabrata* isolates was high in both PC and non-PC, but no significant difference emerged between the groups. Otherwise, resistance to antifungals was rare. Ineffective empirical antifungal treatment was associated with PC in our study. Ineffective antifungal was started before the results from blood cultures were available, but all of these patients who received ineffective antifungal initially received appropriate antifungal after the culture results were disclosed. Relatively many patients (22% of PC and 11% of non-PC cases) initially received an ineffective agent, even though the median duration of the ineffective therapy was short. Half of the inappropriate treatment was prescribed at surgical departments. Treatment with fluconazole or echinocandin as an initial antifungal showed no significant difference between persistent and non-persistent cases.

Neonatal analyses have demonstrated an association between PC and non-albicans *Candida* species.[9,11] Our results reflected no such association in an adult population, consistent with the findings of other studies conducted in adult populations.[12,23] This indicates an overall difference in species distribution between adult and child populations. *C parapsilosis* is a more common cause of candidaemia in children than in adults,[29,30] and this might not be a finding specific to PC *C. albicans* was the leading cause of both PC and non-PC in our study; it is the leading cause of candidaemia overall in Northern Europe.[29,31-33]

Underlying factors, such as malignancies, neutropenia, severe comorbidities and transplantation, have been identified as risk factors for candidaemia.[34] However, these factors were not associated significantly more frequently with PC than non-PC in our study. The overall 30-day mortality rate in our hospital district was 31% during the study period, which is slightly lower than earlier finding in Finland. The one-month case fatality rate was 35% in a population-based study conducted in Finland in 2004-2007.[35] The use of echinocandins has increased as an initial therapy for candidaemia during the same period, and it might have decreased the mortality rate. The overall 30-day mortality rate was similar to figures reported in other Nordic countries: Iceland (30%, 2013), Norway (36%, 2019) and Denmark (37%, 2011 and 43%, 2018).[5,29,31,36] The 30-day mortality was 20.0% in PC and 13.9%

in non-PC in our study, but the difference did not reach statistical significance. Surprisingly, the overall 30-day mortality rate was lower in PC than overall in our hospital district or in general in candidaemia.[2-5] Candidaemia is associated with severe underlying comorbidities, for example malignancies.[36] Sometimes, it is justified to focus on symptomatic treatment and refrain from control blood cultures if the patient is in a terminal phase. Patients who died within five days or had no negative blood cultures taken were excluded from our analysis. When we excluded these patients, it decreased the mortality rate in PC and non-PC groups.

Adherence to guidelines was evaluated with the Equal Candida Score. The score showed an association with mortality, but not with PC. A recent study from Taiwan reported a significant association with survival outcome as well.[37] However, other previous studies have not found a significant difference,[38-40] despite survivors having higher Equal Candida Scores than non-survivors. The patient number was smaller in these studies. The median score was 13.0 in our study. There is still a long way to go to achieve an excellent rating according to ESCMID and IDSA guidelines.

Our study has several potential limitations. The most significant one is the retrospective nature of the analysis. Follow-up blood cultures are strongly recommended, but there were no predesigned routines for follow-up blood cultures during the study period. Monitoring infection clearance from blood cultures is often neglected if a patient responds very well to treatment or if the patient is terminally ill. However, this study provides reliable data over a 10-year study period for adult patients.

In conclusion, the presence of CVC, metastatic infection foci and ineffective empirical antifungal were independent risk factors for PC. Active search for and treatment of metastatic infection foci, and removal of CVC are the key elements for improving patient care and preventing PC.

CONFLICT OF INTEREST

MAH has received lecture fee from MSD and Gilead and conference invitations from Pfizer and MSD. VJA has received lecture fees from Pfizer, MSD, Astellas, Unimedic, Roche, BMS, Biogen and Gilead; has participated as PI to *Varicella zoster* vaccination studies; and has received a study grant for a pneumococcal vaccination study.

AUTHORS' CONTRIBUTION

MAH and VJA conceived the study design. MAH has collected and analysed the data. Both authors drafted the manuscript and approved the final version of the manuscript.

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