An Overview of Candidemia Patients in Tertiary Hospital, Surabaya, Indonesia

Cahya Ayu Pratiwi[a], Prananda Surya Airlangga[b], Pepy Dwi Endraswari[c,d]*

* pepy.dr@fk.unair.ac.id
[a]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[b]Depart*ment of Anesthesiology and Reanimation, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic* Hospital, Surabaya, Indonesia
[c]*Department of Medical Microbiology, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Ac*ademic Hospital, Surabaya, Indonesia
[d]Unit of Clinical Microbiology, Universitas Airlangga Hospital, Surabaya, Indonesia

Abstract

Candidaemia is a bloodstream infection (BSIs) caused by Candida spp. common in hospitalized patients. Candidemia has a high mortality and morbidity. This study aimed to give an idea about incidence, patient characteristics, species and patterns of candida susceptibility, and risk factors in candidaemia patients at Dr. Soetomo Hospital from January to December 2020. This is descriptive research using an observational research design. This study used a medical record instrument for candidemia patients in the inpatient ward of Dr. Soetomo and data in the form of records of blood culture results at the Clinical Microbiology Unit of RSUD Dr. Soetomo Surabaya for the period January-December 2020. The observed variables include; incidence, sex, age, the origin of hospitalization, species distribution, frequency of antifungal sensitivity testing, and risk factors for candidemia. In 12 months, 53 candidemia patients were treated at Dr. Soetomo Hospital. The incidence of candidemia is 1.58 cases per 1000 person-years. Most of them are male (64.15%) and aged less than <1 year (28,30). Most of the medical units at the time of the diagnosis were intensive care units and pediatric wards (28.30%). Candida albicans was the most commonly found species (33.96%), then Candida tropicalis (26.41%) and Candida parapsilosis (24.53%). Two Candida glabrata isolates (40%) were susceptible to caspofungin, and all isolates (100%) of Candida albicans, Candida parapsilosis, Candida rugosa, Candida lusitaniae, Candida tropicalis, Candida dubliniensis, and were susceptible to the antifungals tested. Patients who use the Central Venous Catheter (CVC) have the highest level of risk factor, followed by patients with diabetes mellitus.

Keywords: Candidemia; Candida species; incidence; antifungal susceptibility; risk factor.

1. Introduction

Candidaemia is a bloodstream infection (BSIs) caused by Candida spp. common in hospitalized patients [1][2]. Candidemia is one of the problems in intensive care in developing and developed countries. Candidemia can lead to prolonged patient care time, high healthcare costs, substantial morbidity, and up to 30% of hospital deaths [3][4][5]. In the United States, Candida spp ranks fourth as a pathogen that often causes nosocomial bloodstream infections with a percentage of 8-10% [6]. According to conservative estimates, about 25,000 candidemia cases occur nationally yearly and more than 50,000 lead to death [7].

According to Dr. Soetomo Hospital data, in January-March 2015, fungal microbes were found in 29 patient blood specimens, of which 93.09% were Candida spp. The most common Candida species found

was Candida famata, as much as 34.48% [8]. The intensive observation room is the treatment room that produces the most fungal microbes from blood samples (26.09%), followed by the neonate ward and ICU at 17.24% and 10.35%, respectively [8].

Despite differences in the incidence of candidaemia in different countries, the incidence of candidaemia in America has decreased [3]. From 2008 to 2013, the incidence of candidemia fell before stabilizing at around 9 cases per 100,000 people from 2013 to 2017 [3][9]. Improving health services, such as care and maintenance of catheters, can cause a decrease in the incidence of candidaemia [9].

The results of various studies indicate several risk factors for candidemia, including surgery, neonates, experiencing kidney failure or undergoing hemodialysis, use of broad-spectrum antibiotics, ventilators, central venous catheters (CVC), total parenteral nutrition (TPN), patients hospitalized in the ICU for a long time, abuse of intravenous drugs, use of corticosteroids or other immunosuppressant drugs, people with diabetes, and damage to the skin or digestive tract [10][11].

Until now, research on candidemia has been mainly done in developed countries, while the incidence of candidemia varies across the globe. Based on these findings, more research on candidemia is required, particularly in developing countries. It is hoped that this research will provide the latest information on the incidence, patient characteristics, species and patterns of candida susceptibility, and risk factors of candidemia at Dr. Soetomo Hospital, Surabaya as a reference in formulating policies to improve the management of patients treated in inpatient installations.

2. Methods

2.1 Study Design

This research is descriptive research. We used data from the recods of blood cultue results from the Clinical Microbiology Unit and inpatients medical record with candidemia in Dr. Soetomo Hospital from January 2020 until December 2020. All medical records containing patient demographic data, the origin of hospitalization species distribution, frequency of antifungal sensitivity, and risk factors were collected and recorded. This research was carried out from September 2021 to May 2022. The population in this study were all candidemia patients in the inpatient Dr. Soetomo Hospital period January-December 2020. The sample of this study were all inpatients with candidemia at Dr. Soetomo Hospital for the period January-December 2020, which was taken by total population sampling, namely the technique of taking all samples that met the inclusion criteria.

2.2 Statistical Analysis

Data were analyzed with Microsoft Excel and presented in a frequency table with the percentage of each variable which was then converted into a descriptive form.

2.3 Ethical Acceptance

Dr. Soetomo Hospital's Health Research Ethics Committee approved this study on September 7, 2021, with certificate number 0579/LOE/301.4.3/IX/2021.

3. Results and Discussion

We report a 1-year descriptive study on candidaemia in RSUD Dr. Soetomo. This study provides an overview of the incidence, patient characteristics, species distribution, species sensitivity patterns, and risk factors in candidemia patients at Dr. Soetomo Hospital. Based on the search for data in the microbiology

unit of Dr. Soetomo Hospital, 55 patients found Candida spp. in the blood of the first isolate. Subsequently, the medical records were searched for the 55 candidemia patients. Based on the search for 55 medical records, two incomplete medical records had to be excluded. After going through the selection process, 53 medical records were obtained that were complete and could be researched. In this study, the number of hospitalized patients in 2020 was 33,495 patients. So, the incidence of candidemia in the inpatient Dr. Soetomo Hospital from January to December 2020 was 1.58 cases per 1000 people/year. The results obtained in this study are almost the same as those in Brazil, where the incidence of candidemia was reported to be 1.54 cases per 1000 people/year [12]. However, different results were obtained from several other countries, namely Croatia, China, and spain with 0.69; 0,32; 0,92 cases per 1000 people/year respectively [2][13][14]. The incidence of candidemia varies greatly depending on hospital characteristics, geographic area, and patient population. According to some literature, although different candidemia incidence results in each country, the overall candidemia incidence has decreased yearly [3][9]. Improving health services, such as care and maintenance of catheters, can cause a decrease in the incidence of candidaemia [3][9].

Table 1. The Characteristic Patients

	Category	**Total, n (%)**
Sex	Male	34 (64,15%)
	Female	19 (35,85%)
Age	<1 years	15 (28,30%)
	1-19 years	12 (22,64%)
	20-44 years	8 (15,10%)
	45-64 years	13 (24,53%)
	≥65 years	3 (9,43%)
Medical Units	Intensive Care	15 (28,30%)
	Pediatric Wards	15 (28,30%)
	Medical Wards	14 (26,42%)
	Surgery Wards	8 (15,09%)
	Obstetric and Gynecology Wards	1 (1,89%)

Based on Table 1, cases of candidemia were more common in males (64.15%) compared to females (35.85%). Males have the highest incidence of candidemia, even after controlling for demographic variables, and these differences persist across all racial groups and adult ages [15]. Women usually get non-invasive candidiasis, especially vaginal candidiasis, but the number of bloodstream infections in women is less than in men. Currently the reason for this incidence difference in gender is unknown [3]. This study is similar with several previous studies, including the research of Toda et al and Mareković et al. The incidence rate by sex in different countries is quite varied. However, in several other previous studies regarding candidemia, gender was not a predictor of candidemia [16].

The most distribution of age groups in this group is the age group <1 year (28.30%), as shown in Table 1. It is also in line with Nugraheni et al in her research on Candidemia patients at the Dr. Kariadi Hospital [17]. Children aged <1 year are susceptible to Candida infection due to weak immune systems [18]. However, different results were obtained in the research of Toda et al where in their research it was stated that the highest age was in the group 65 years and was only followed by the age group <1 year [3]. This difference in results may occur because candidemia can happen in all ages who receive hospital treatment.

As shown in Table 1, the majority of the Candida spp. isolated from the ICU (28.30%). This study was similar to other studies in that candidemia is more prevalent among ICU patients [10][19]. The candidemia prevalence is seven times more common in the ICU than in other inpatient settings [6]. According to several European surveys, 40-50% of candidemia patients are in intensive care [2]. Many studies have discussed ICU hospitalization and candidemia risk factors [15][20]. Candidemia is more common in patients treated in the ICU due to immunocompromised conditions, multiple invasive procedures, use of broad-spectrum antibiotics and immunosuppressive drugs [20]. Pediatric ward is also the location of hospitalization with the most candidemia found. Candidemia is more common in patients in pediatric wards due to low immunity in children and a high number of immunosuppressive treatments due to neoplastic disease, transplantation, or autoimmune conditions [21]. In this study, as many as 28.30% of patients came from pediatric wards.

Table 2. Candida Species Distribution

Candida Species	Frequency	Persentage
Candida albicans	18	33,96%
Candida glabrata	5	9,43%
Candida parapsilosis	13	24,53%
Candida tropicalis	14	26,41%
Candida lusitaniae	1	1,89%
Candida dubliniensis	1	1,89%
Candida rugosa	1	1,89%
Total	**53**	**100%**

Based on Table 2, candidemia patients in 2020 found 53 Candida isolates with seven species. Candida albicans was the leading cause (33.96%), while Candida tropicalis (26.41%) and Candida parapsilosis (24.53%) were the most common candida spesies among non-albicans Candida. This study was similar to previous, including the Resultanti research, in which Candida albicans was found most frequently in patients at Cipto Mangunkusumo Hospital [22]. In this study, Candida tropicalis is the second most common cause. Candida tropicalis appears to be the most common non-albicans Candida species in tropical countries [23]. This is in accordance with the research of Tan et al who found that from year to year, there was an increase in Candida tropicalis in India, Singapore, and Thailand [23]. In a study by Huiying et al which involved 198 candidemia patients, a tertiary university-affiliated hospital in southwest China stated that Candida tropicalis and Candida parapsilosis were the most prevalent Candida species after Candida albicans [13].

Although Candida albicans is the most prevalent cause of candidemia on a global scale, its prevalence is decreasing. This is inversely proportional to the annual rise in non-albicans Candida incidence [24]. In this study, the proportion of non-albicans Candida reached 66.05%. The surge in non-albicans Candida could be due to increasing azole antifungals, especially fluconazole as therapy and prophylaxis [25]. The extermination of Candida albicans with fluconazole causes the emergence of non-albicans resistant or less sensitive Candida species, thereby altering the annual incidence of Candida albicans and non-albicans [25].

Table 3. Frequency of Antifungal Susceptibility

	Fluconazole	Voriconazole	Amphotericin B	Micafungin	Caspofungin	Flucytosine
Candida albicans (18)	18/18 (100%)	16/16 (100%)	16/16 (100%)	18/18 (100%)	18/18 (100%)	18/18 (100%)
Candida glabrata (5)	NT	5/5 (100%)	5/5 (100%)	5/5 (100%)	2/5 (40%)	5/5 (100%)
Candida parapsilosis (13)	13/13 (100%)	13/13 (100%)	13/13 (100%)	12/12 (100%)	12/12 (100%)	13/13 (100%)
Candida tropicalis (14)	11/11 (100%)	14/14 (100%)	14/14 (100%)	11/11 (100%)	11/11 (100%)	10/10 (100%)
Candida lusitaniae (1)	NT	1/1 (100%)	1/1 (100%)	NT	NT	1/1 (100%)
Candida dubliniensis (1)	NT	1/1 (100%)	1/1 (100%)	NT	NT	1/1 (100%)
Candida rugosa (1)	NT	1/1 (100%)	1/1 (100%)	NT	NT	1/1 (100%)

Note. NT= Not Tested

Systemic antifungal administration based on timely and accurate identification and antifungal sensitivity testing is crucial for optimal implementation. Based on Table 3, 100% of Candida albicans, Candida parapsilosis, and Candida tropicalis isolates were susceptible to the antifungals fluconazole, amphotericin B, voriconazole, caspofungin, micafungin, and flucytosine. Similar results were found in the study of Xiao et al which stated that none of the isolates of Candida albicans, Candida parapsilosis, and Candida tropicalis that were resistant to antifungals were tested [20]. The isolates of Candida lusitaniae, Candida dubliniensis, and Candida rugosa were found to be 100% susceptible to the antifungal voriconazole, amphotericin B, and flucytosine. The isolates of Candida glabrata were found to be 100% sensitive to the antifungal voriconazole, amphotericin B, micafungin, and flucytosine and 40% sensitive to the antifungal caspofungin. The emergence of echinocandin-resistant Candida glabrata isolates, including caspofungin, has been well documented, and these findings are associated with poorer clinical outcomes [26]. Resistance of Candida glabrata to echinocandin therapy is linked to mutations in FKS [26].

Candida glabrata also has a high level of antifungal resistance to fluconazole, which has remained relatively stable over the last two decades [5][9]. Candida glabrata's resistance to the fluconazole is associated with decreased azole group permeability or up-regulation of P450 enzymes in cell membranes [27]. However, it is unfortunate that in this study no data were obtained regarding the sensitivity test of Candida glabrata isolates to fluconazole.

Based on IDSA recommendations, fluconazole antifungal therapy is used in patients with relatively mild and stable clinical conditions who have not been exposed to previous azole antifungal agents and have an infection with Candida parapsilosis [28]. While echinocandins are used in patients with more severe clinical conditions, prior exposure to azole antifungals and infection by Candida glabrata [28]. Amphotericin B antifungal therapy is chosen in patients who are already intolerant to azole antifungals and echinocandins [28].

Table 4. Suspected Risk Factors Associated Candidemia

Risk Factors	Frequency	Persentage
Malignancy	11	20,75%
Solid tumor	7	13,20%
Blood Cancer	4	7,55%
Surgery	15	28,30%
Abdominal	13	24,53%
non abdominal	2	3,77%
Use of broad spectrum antibiotics ≥14 hari	23	43,40%
Ceftriaxone	9	16,98%
Metronidazole	5	9,44%
Amikacin	3	5,66%
Meropenem	2	3,77%
Levofloxacin	2	3,77%
Ceftazidime	1	1,89%
Ampicillin	1	1,89%
Use of Central Venous Catheters (CVC)	33	62,26%
<7 days	10	18,87%
≥7 days	23	43,39%
Use of Total Parenteral Nutrition (TPN)	20	37,74%
<7 days	5	9,43%
≥7 days	15	28,30%
Patients with diabetes mellitus	25	47,17%
Corticosteroid therapy ≥14 days	9	16,98%
Neonate	8	15,09%
Elderly	9	16,98%

Based on table 4, the most common risk factor for candidemia found in Dr. Soetomo Hospital inpatients is the use of CVC, with the highest duration of use for seven days (43.39%), followed by 25 patients with diabetes mellitus (47.17%). Most of the candidemia patients were inpatients at Dr. Soetomo Hospital had more than one risk factors.

Several risk factors for candidemia have been studied in various countries. Many risk factors mentioned in these studies include malignancy, surgery, use of broad-spectrum antibiotics for 14 days, use of CVC, use of TPN, people with diabetes mellitus, corticosteroid therapy 14 days, neonates, and the elderly [7][9]. The use of CVC was the highest risk factor for candidemia in this study, as in previous studies [2][10].The use of CVC is one of the risk factors for candidemia because the catheter used is contaminated with Candida spp. No studies are designed to assess the outcome after CVC removal in candidemia patients [29][30]. Although careful analysis could not identify a significant outcome of CVC removal, other studies have found that catheter removal at any time point resulted in reduced mortality and higher clinical success rates [10]. The debate regarding CVC removal in candidemia patients will continue, but IDSA recently issued clinical practice guidelines for managing invasive candidiasis, which recommend the removal of the CVC as

soon as possible if a catheter source is suspected [28]. On the other hand, people with diabetes mellitus are also the second most common candidemia risk factor in this study. Research by Toda et al also stated that one-third (33%) of candidemia cases in four locations in the United States occurred in people with diabetes mellitus [3]. Several factors cause susceptible diabetes mellitus patients to suffer from candidemia, namely fungal adhesion to the surface of epithelial cells, impaired neutrophil activity, low host defense mechanism, microvascular degeneration, higher salivary glucose levels, and reduced salivary flow [2].

4. Conclusion

During the one-year observation period from January-December 2019, 53 candidemia patients were treated at RSUD Dr. Soetomo Surabaya. Most of them are men with the highest age group of <1 year. The most frequently found species is Candida Albicans. Most of the Candida isolates were susceptible to antifungal agents. Central Venous Catheters (CVC) was the most risk factor for candidaemia in this study.

Acknowledgements

The author would like to express their deepest gratitude to all staff of the health research ethics committee, medical record data officers, and all staff of the Clinical Microbiology Laboratory of Dr. Soetomo for their help during data collection so that this research can take place and achieve its objectives.

References

[1] D. M. Barter, H. L. Johnston, S. R. Williams, S. V Tsay, S. Vallabhaneni, and W. M. Bamberg, “Morbidity and Mortality Weekly Report Candida Bloodstream Infections Among Persons Who Inject Drugs-Denver Metropolitan Area, Colorado, 2017-2018,” vol. 68, no. 12, pp. 2017–2018, 2019.

[2] I. Mareković, S. Pleško, V. Rezo Vranješ, Z. Herljević, T. Kuliš, and M. Jandrlić, “Epidemiology of Candidemia: Three-Year Results from a Croatian Tertiary Care Hospital,” J. Fungi, vol. 7, no. 4, p. 267, 2021.

[3] M. Toda et al., “Population-Based Active Surveillance for Culture-Confirmed Candidemia — Four Sites, United States, 2012–2016,” MMWR Surveill. Summ., vol. 68, no. 8, pp. 1–17, 2019.

[4] S. Strollo, M. S. Lionakis, J. Adjemian, C. A. Steiner, and D. R. Prevots, “Epidemiology of Hospitalizations Associated with Invasive,” Emerg. Infect. Dis., vol. 23, no. 1, pp. 7–13, 2017.

[5] A. A. Cleveland et al., “Changes in incidence and antifungal drug resistance in candidemia: Results from population-based laboratory surveillance in Atlanta and Baltimore, 2008-2011,” Clin. Infect. Dis., vol. 55, no. 10, pp. 1352–1361, 2012.

[6] N. S. Raja, “Epidemiology, risk factors, treatment and outcome of Candida bloodstream infections because of Candida albicans and Candida non-albicans in two district general hospitals in the United Kingdom,” Int. J. Clin. Pract., vol. 75, no. 1, pp. 1–8, 2020.

[7] A. M. Kullberg BJ, “Invasive candidiasis,” Nat. Rev. Dis. Prim., vol. 4, pp. 1445–1456, 2015.

[8] A. Ridhoi, “Mikroba Jamur Dari Spesimen Darah Periode Januari-Maret 2015 di Instalasi Mikrobiologi Klinik RSUD Dr Soetomo Surabaya,” 2015.

[9] A. A. Cleveland et al., “Declining incidence of candidemia and the shifting epidemiology of Candida resistance in two US metropolitan areas, 2008-2013: Results from population-based surveillance,” PLoS One, vol. 10, no. 3, pp. 2008–2013, 2015.

[10] L. Tadec et al., “Epidemiology, risk factor, species distribution, antifungal resistance and outcome of Candidemia at a single French hospital: A 7-year study,” Mycoses, vol. 59, no. 5, pp. 296–303, 2016.

[11] T. M. Dixit, Deepali PharmD, BCPS, BCCCP, FCCM; Jen, Polly PharmD, BCPS, BCIDP, AAHIVP; Maxwell, Tyler D. BS, PharmD; Smoke, Steven PharmD, BCPS, BCIDP; McCracken, James Andrew PharmD; Cardinale-King, Maria PharmD,

BCCCP; Haribhakti, Aditi PharmD Candidate; Pat, "Risk Factors and Clinical Outcomes of Candidemia Associated With Severe COVID-19," pp. 1–10, 2022.

[12] M. Nucci, G. Barreiros, L. F. Guimarães, V. A. S. Deriquehem, A. C. Castiñeiras, and S. A. Nouér, "Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic," Mycoses, vol. 64, no. 2, pp. 152–156, 2021.

[13] Z. Huiying et al., "Clinical characteristics and predictors of mortality in patients with candidemia in intensive care unit," Zhonghua Wei Zhong Bing Ji Jiu Yi Xue, vol. 30, no. 10, pp. 929–932, 2018.

[14] J. Pemán et al., "Epidemiology, species distribution and in vitro antifungal susceptibility of fungaemia in a Spanish multicentre prospective survey," J. Antimicrob. Chemother., vol. 67, no. 5, pp. 1181–1187, 2012.

[15] L. R. Asmundsdottir and H. Erlendsdottir, "Drug Resistance in Iceland , 2000 to 2011," vol. 51, no. 3, pp. 841–848, 2013.

[16] D. K. Indrawan, A. H. Pudjiadi, and A. L. Latief, "Insidens Kandidemia di Paediatric Intensive Care Unit Rumah Sakit Dr. Cipto Mangunkusumo," Sari Pediatr., vol. 18, no. 3, p. 182, 2017.

[17] R. Nugraheni, "FAKTOR RISIKO KANDIDEMIA DI RSUP Dr KARIADI SEMARANG," 2012.

[18] D. M. Hassan, R. H. A. Yousef, W. A. A. Elhamed, A. A. Ali, and L. A. Madkour, "Candidemia in the neonatal intensive care unit: Insights on epidemiology and antifungal drug susceptibility patterns," Arch. Pediatr. Infect. Dis., vol. 7, no. 1, pp. 1–6, 2019.

[19] H. Wang, Y. Xu, and P. Hsueh, "Epidemiology of candidemia and antifungal susceptibility in invasive Candida species in the Asia-Pacific region," vol. 11, pp. 1461–1477, 2016.

[20] Z. Xiao, Q. Wang, F. Zhu, and Y. An, "Epidemiology, species distribution, antifungal susceptibility and mortality risk factors of candidemia among critically ill patients: A retrospective study from 2011 to 2017 in a teaching hospital in China," Antimicrob. Resist. Infect. Control, vol. 8, no. 1, pp. 1–7, 2019.

[21] J. Fu, Y. Ding, Y. Jiang, S. Mo, S. Xu, and P. Qin, "Persistent candidemia in very low birth weight neonates: Risk factors and clinical significance," BMC Infect. Dis., vol. 18, no. 1, pp. 4–9, 2018.

[22] Resultanti, "Faktor Risiko Kandidemia Pada Pasien Sepsis Non Neutropenia," 2016.

[23] B. H. Tan et al., "Incidence and species distribution of candidaemia in Asia : a laboratory- based surveillance study," pp. 946–953, 2015.

[24] W. Zhang, X. Song, H. Wu, and R. Zheng, "Epidemiology, risk factors and outcomes of Candida albicans vs. non-albicans candidaemia in adult patients in Northeast China," Epidemiol. Infect., vol. 147, 2019.

[25] K. F. Kalista, L. K. Chen, R. Wahyuningsih, and C. M. Rumende, "Karakteristik Klinis dan Prevalensi Pasien Kandidiasis Invasif di Rumah Sakit Cipto Mangunkusumo," J. Penyakit Dalam Indones., vol. 4, no. 2, p. 56, 2017.

[26] B. D. Alexander et al., "Increasing echinocandin resistance in candida glabrata: Clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations," Clin. Infect. Dis., vol. 56, no. 12, pp. 1724–1732, 2013.

[27] R. Prasad, A. H. Shah, and M. K. Rawal, "Antifungals: Mechanism of action and drug resistance," Adv. Exp. Med. Biol., vol. 892, pp. 327–349, 2016.

[28] P. G. Pappas et al., "Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America," Clin. Infect. Dis., vol. 62, no. 4, pp. e1–e50, 2015.

[29] O. A. Cornely et al., "ESCMID guideline for the diagnosis and management of Candida diseases 2012: Non-neutropenic adult patients," Clin. Microbiol. Infect., vol. 18, no. SUPPL.7, pp. 19–37, 2012.

[30] S. Janum and A. Afshari, "Central venous catheter (CVC) removal for adult patients with candidaemia," Cochrane Database Syst. Rev., vol. 2014, no. 7, 2014.