

The search for endocarditis in patients with candidemia: a systematic recommendation for echocardiography? A prospective cohort

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Abstract Most current guidelines do not recommend systematic screening with echocardiography in patients with candidemia, as *Candida* infective endocarditis (CIE) is considered an uncommon disease. During the study period, we recommended echocardiography systematically to all candidemic patients that did not have contraindications and accepted to participate in the study. We intended to assess the incidence of unrecognized CIE in adult patients with candidemia. Our institution is a tertiary teaching hospital in which we follow all patients with candidemia. From January 2007 to October 2012, echocardiography was systematically recommended to suitable candidates. We recorded 263 cases of candidemia in adult patients. Echocardiography was not performed in 76 of these patients for the following reasons:

patients had died when blood cultures became positive (17), patients were critically or terminally ill (38), or the patient or physician refused the procedure (21). The remaining 187 patients constitute the basis of this report. CIE was diagnosed in 11 cases (4.2 % of the whole candidemic population and 5.9 % of the population with echocardiographic study). The results of transthoracic echocardiography (TTE) suggested infective endocarditis (IE) in 5/172 patients (2.9 %), and the result of transesophageal echocardiography (TEE) was positive in 10/87 (11.5 %). Among 11 confirmed cases of CIE, the disease was clinically unsuspected in three patients. At least 4.2 % of all candidemic patients have CIE. CIE is frequently clinically unsuspected and echocardiography is required to demonstrate a high proportion of cases.

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Abbreviations

CIE	<i>Candida</i> infective endocarditis
IE	Infective endocarditis
TTE	Transthoracic echocardiography
TEE	Transesophageal echocardiography
GAME	Grupo de Apoyo al Manejo de la Endocarditis
SAB	<i>Staphylococcus aureus</i> bacteremia

Introduction

Current guidelines recommend systematic screening with echocardiography in all patients with clinically suspected infective endocarditis (IE), but also in patients with bacterial bloodstream infections (BSI) caused by Gram-positive bacteria, particularly those caused by *Staphylococcus aureus*, irrespective of a clinical suspicion of endocarditis [1, 2]. Echocardiography in that population frequently demonstrates the presence of clinically unsuspected IE.

The recommendation to apply echocardiography systematically in other BSI is far from clear. The incidence of *Candida* infective endocarditis (CIE) in candidemic patients has been evaluated only in a retrospective study by Nasser et al. [3], who analyzed patients with prosthetic heart valves. We were unable to find studies investigating the yield of a systematic use of echocardiography to rule CIE in patients with candidemia [4]. The incidence of clinically unsuspected CIE is unknown.

We performed a prospective study to assess the yield of routine echocardiography in an unselected cohort of adult patients with candidemia.

Patients and methods

Our institution is a 1,550-bed tertiary teaching hospital. During the study period, its catchment population was 650,000–750,000 inhabitants. The hospital is a referral center with an active major heart surgery unit and several transplantation programs. Our institution also has a cooperative multidisciplinary group for the prospective study of IE (GAME, Grupo de Apoyo al Manejo de la Endocarditis).

This study was reviewed and approved by the Ethics Committee of the Hospital Universitario Gregorio Marañón.

Study period and patient selection

The GAME endocarditis study group has systematically followed all patients with candidemia at our institution since 2007. A microbiological endocarditis alert is activated when the microbiology department detects a patient with candidemia, and a specialized nurse and an infectious diseases

specialist evaluate the patient's clinical condition and routinely recommend transesophageal echocardiography (TEE) to the attending physician and the patient. The recommendation is made independently of the clinical suspicion of endocarditis, which is based mainly on the presence of valve disease, prosthetic endovascular material, or persistent candidemia. Patients are followed up until discharge.

Data for all patients with candidemia between 2007 and October 2012 were registered in a BSI database and an IE database.

Echocardiography

The type of echocardiography was chosen by the cardiologist. Usually, a transthoracic echocardiography (TTE) was performed first, and then a TEE was considered. But when the suspicion of IE was high, some cardiologists proceeded directly to the TEE, due to its higher sensitivity. The routine recommendation to exclude endocarditis was TEE. Depending on whether consent was given or not for TEE, the patient's clinical status, the presence of prosthetic material, and whether a good window was obtained with TTE, a TTE, a TEE, or both were done. Patients gave their informed consent for TEE. As TTE was considered a routine test, no formal signed consent was required.

Processing in the microbiology laboratory

Blood cultures were obtained using standard procedures and processed using the BACTEC 9240 blood culture system until 2009 (Becton Dickinson, Sparks, MD, USA) and the BD Bactec FX system from 2010 onwards (Becton Dickinson, Sparks, MD, USA). All systems were used according to the manufacturer's instructions. *Candida* species were identified by ID32 (bioMérieux, Marcy L'Étoile, France).

Clinical criteria and definitions

We defined an episode of candidemia as the isolation from ≥ 1 blood culture of a microorganism belonging to the genus *Candida*. Candidemia was considered persistent when ≥ 1 blood culture obtained ≥ 3 days after the first one yielded the same *Candida* species.

We recorded the following clinical data: demographic characteristics, underlying diseases (in particular, valve disease), valvular prosthesis, persistent candidemia, and *Candida* species. In cases of confirmed CIE, we recorded the type of echocardiography performed, treatment, and outcome.

The diagnosis of CIE was made according to the modified Duke criteria [5]. Regarding the echocardiographical criteria, all patients had mobile masses compatible with endocardial vegetations. If the vegetations were not located on valves, but were mural vegetations, they should not be

implanted in central catheters or should persist after withdrawal of the catheter in order to be considered diagnostic of endocarditis.

All cases of endocarditis were discussed at the GAME study group in order to evaluate if they fulfilled endocarditis criteria and, if so, they were included in the endocarditis database.

Statistical analysis

We analyzed the yield of echocardiography for the diagnosis of CIE, in particular that of TEE.

Associations between variables were evaluated using the χ^2 test for categorical variables, the *t*-test for normally distributed continuous variables, and the Mann–Whitney test for non-parametric comparisons. A *p*-value < 0.05 was considered significant. Multivariate analysis was performed using logistic regression. Variables with a *p*-value \leq 0.1 in the univariate analysis were included in the multivariate model.

The statistical analysis was performed with SPSS 16.0 (SPSS, Chicago, IL, USA).

Results

From January 2007 to October 2012, we recorded 263 episodes of candidemia in adult patients in our hospital, which represented 7.5 % of all BSI. Echocardiography was not performed in 76 cases and our results are based on data from the remaining 187 patients. Reasons for not performing echocardiography were as follows: patients had been discharged or had died when the blood culture became positive (17), patients were critically or terminally ill (38), and the patient or the physician refused the procedure (21). The only independent significant difference between patients that underwent an echocardiogram and those that did not was a higher prevalence of persistent candidemia among the former [33.7 % vs. 10.2 %, *p* < 0.01, relative risk (RR) 4.51 (1.83–11.11)]. None of the eligible patients who did not undergo echocardiography presented with IE or a recurrent episode of candidemia during the follow-up period.

Characteristics of the population

Table 1 shows the general characteristics of the population. Twelve patients (6.4 %) had a valvular prosthesis, 2 (1.1 %) had pacemakers, 26 (13.9 %) had non-prosthetic valve disease, 63 (33.7 %) had persistent candidemia, and 98 (52.4 %) had none of these factors. Fourteen patients presented >1 risk factor.

Table 1 General characteristics of the study population

Echocardiogram performed (187)	
Male gender	119 (63.6 %)
Age, years, mean (\pm SD)	65.2 (\pm 14.8)
Charlson (mean \pm SD)	3.3 (\pm 2.5)
Charlson with age (mean \pm SD)	5.4 (\pm 2.7)
Underlying disease	
Cancer	77 (41.2 %)
Cardiovascular	27 (14.4 %)
Neurological	15 (8 %)
Diabetes	10 (5.3 %)
Liver	9 (4.8 %)
Hemodialysis or hemodiafiltration	13 (6.9 %)
Other	43 (23 %)
None	6 (3.2 %)
Area of admission	
Medical	82 (43.9 %)
Surgical	64 (34.2 %)
Intensive care	41 (21.9 %)
Percentage of positive blood cultures ^a	77.2 % (\pm 25.4)
Persistent candidemia	63 (33.7 %)
<i>C. albicans</i> (%) vs. non- <i>albicans</i>	91 (48.7 %) vs. 96 (51.3 %)
Valvular prosthesis ^b	
Mitral prosthesis	8 (4.3 %)
Aortic prosthesis	5 (2.7 %)
Tricuspid prosthesis	1 (0.5 %)
Pacemaker	2 (1.1 %)
Previous valve disease (prosthesis not included)	26 (13.9 %)
No persistent candidemia, prosthesis, pacemaker, or valve disease	98 (52.4 %)
In-hospital death	57 (30.5 %)

^a Proportion of blood cultures that grew *Candida* among those drawn

^b One patient had both a mitral and a tricuspid prosthesis, and one patient had both a mitral and an aortic prosthesis

Type of echocardiogram

One or more echocardiograms were performed in 187 patients. Of these, 100 patients (53.5 %) underwent TTE only, 15 (8 %) underwent TEE only, and 72 patients (38.5 %) underwent both. The median time from blood culture positivity to echocardiography was 5 days [interquartile range (IQR), 3–7.5 days].

When comparing patients that underwent a TEE with those who did not, the only independent significant difference was the presence of valvular prosthesis, which was more prevalent among the former [12.6 % vs. 1 %, relative risk (RR) 13.6 (confidence interval [CI] 1.7–109.3)].

Table 2 Characteristics of patients with *Candida* endocarditis

Age/ sex	Date	Underlying condition	Risk factor	Number of persistent candidemia positive blood cultures	Echo performed	Diagnosis echo	Valve	Etiology	Heart sur- gery	Complications	Medical therapy	Days on antifungals	Clinical outcome at discharge
62/M	2007	Valvular prosthesis	Previous candidemia	5/5, 100 %	TEE	TEE	Aortic, prosthetic	<i>C. parapsilosis</i>	Died before surgery	Hemorrhagic stroke	Fluconazole	1	Attributable death
48/M	2007	AIDS	Hemodialysis	3/3, 100 %	TTE	TTE	Aortic native	<i>C. parapsilosis</i>	Aortic prosthesis	Ischemic stroke, renal failure	Fluconazole Caspofungin + voriconazole L-Ampho + fluconazole	68 + secondary prophylaxis (fluconazole)	Alive
72/F	2007	Valvular prosthesis, renal failure	Previous antibiotics	2/3, 67 %	TEE	TEE	Right atrium	<i>C. parapsilosis</i>	Rejected for surgery	Cardiogenic shock	Caspofungin Fluconazole	30	Dead
72/M	2007	Neoplasm	Previous candidemia, previous antibiotics, abdominal surgery	6/6, 100 %	TTE + TEE	TTE + TEE	Tricuspid native	<i>C. tropicalis</i>	Tricuspid prosthesis	Pulmonary involvement, renal failure	Fluconazole Caspofungin Fluconazole	71	Dead
52/M	2007	Neoplasm	Abdominal surgery, CVC	5/5, 100 %	TTE + TEE	TEE	Right atrium	<i>C. guilliermondii</i>	Not necessary	No	Voriconazole Caspofungin	27	Alive
73/F	2008	Valvular prosthesis	Cardiac surgery, CVC	3/3, 100 %	TTE + TEE	TEE	Right atrium	<i>C. albicans</i>	Rejected for surgery	Possible hepatic embolism	Fluconazole Caspofungin L-Ampho	21	Dead
72/M	2009	Neoplasm aortic vascular prosthesis	Hemodialysis	7/9, 78 %	TTE + TEE	TTE + TEE	Mitral native	<i>C. albicans</i>	Mitral prosthesis	Postsurgical hemorrhage, hemorrhagic stroke	Caspofungin Fluconazole	33	Attributable death
71/M	2009	Neoplasm	Abdominal surgery, CVC duodenal leak	8/9, 89 %	TTE + TEE	TTE + TEE	Aortic and mitral native	<i>C. glabrata</i>	Aortic and mitral prosthesis	Postsurgical hemorrhage, postsurgical candidemia	Caspofungin + 5 flucytosine	114, including secondary prophylaxis (caspofungin)	Alive
35/M	2009	AIDS, Whipple	CVC, parenteral nutrition, previous antibiotics	1/4, 25 %	TTE + TEE	TTE + TEE	Tricuspid native	<i>C. albicans</i>	Rejected for surgery	Retinitis	Caspofungin + fluconazole	39	Alive
69/F	2010	Neoplasm	Abdominal surgery, antibiotics	2/4, 50 %	TEE	TEE	Right atrium	<i>C. albicans</i>	Not necessary	Endophthalmitis	Fluconazole Micafungin + fluconazole	53	Alive
81/M	2011	Previous endocarditis, valvular prosthesis neoplasm	Previous antibiotics	5/6, 83 %	TEE	TEE	Aortic valve, prosthetic	<i>C. albicans</i>	Rejected for surgery	Multiorgan failure	Fluconazole Caspofungin + fluconazole Anidulafungin	9	Attributable death

M male, *F* female, *AIDS* acquired immunodeficiency syndrome, *TEE* transesophageal echocardiography, *TTE* transthoracic echocardiography, *L-Ampho* liposomal amphotericin B, *CVC* central venous catheter

Yield of echocardiography

Of the 187 patients who underwent echocardiography, 11 (5.9 %) had findings that indicated IE. The diagnostic yield of IE in patients with candidemia was 2.9 % (5/172) for TTE and 11.5 % (10/87) for TEE. Left valves were the most commonly affected (five patients), followed by four cases of atrial endocarditis. *C. albicans* and *C. parapsilosis* were responsible of the majority of the endocarditis cases (8/11, 72.7 %) (Table 2).

Among the 11 patients with CIE, one had only a TTE performed, four had only a TEE performed, and six had both TTE and TEE. All patients presented mobile masses that fulfilled Duke's criteria. CIE was diagnosed using TTE in 5 out of 7 cases of endocarditis in which it was performed (71.4 %); TEE was positive in all ten cases of CIE in which it was performed (100 %). Of the six patients with endocarditis who underwent both TTE and TEE, two cases of CIE (33.3 %) were diagnosed only using TEE.

The prevalence of CIE among patients with a valvular prosthesis was 33 % (4/12). In patients with at least one risk factor (valvular prosthesis, persistent candidemia, or previous valve disease), the prevalence was 9 %; in those without risk factors, it was 3.1 % ($p = 0.12$). Nevertheless, thanks to the use of routine echocardiography in patients with candidemia, CIE was diagnosed in three cases with neither endovascular predisposing conditions nor persistent candidemia (Table 2). Two of these patients presented mural vegetations that were not related with catheters or persisted after withdrawal, and, so, fulfilled Duke's criteria.

Comparison between patients with and without endocarditis

In an attempt to determine whether echocardiography could be avoided in selected patients with a low risk of endocarditis, we compared patients with and without endocarditis who had undergone echocardiography. No statistically significant differences were observed between patients with or without CIE according to clinical or microbiological predisposing factors (Table 3), except for the presence of a valvular prosthesis, which was significantly more frequent among patients with IE (36.4 % vs. 4.5 %, $p < 0.01$). When the subset of patients with valvular prosthesis was excluded, it was not possible to predict which patients would have CIE.

Discussion

Routine echocardiography in patients with candidemia reveals a higher incidence of CIE than expected, particularly in patients examined using TEE (11.5 % of cases of CIE). As many as 30 % of cases of CIE were found

Table 3 Comparison of patients with or without *Candida* infective endocarditis (CIE)

N=187	No endocarditis (n=176)	Endocarditis (n=11)	p-Value
Male gender	111 (63.6 %)	8 (70.0 %)	0.75
Age, years, mean (\pm SD)	65.2 (\pm 14.9)	64.9 (\pm 13)	0.95
Charlson	3.3 \pm 2.4	4.7 \pm 3.5	0.20
Charlson with age	5.3 \pm 2.6	6.9 \pm 3.3	0.05
Underlying disease			0.35
Cancer	73 (41.5 %)	4 (36.4 %)	
Cardiovascular	23 (13.1 %)	4 (36.4 %)	
Neurological	15 (8.5 %)	0 (0 %)	
Diabetes	10 (5.7 %)	0 (0 %)	
Liver	9 (5.1 %)	0 (0 %)	
Hemodialysis or hemodiafiltration	11 (6.3 %)	2 (18.2 %)	
Other	40 (22.7 %)	3 (27.3 %)	
None	6 (3.4 %)	0 (0 %)	
Percentage of positive blood cultures ^a	76.9 (\pm 25.5)	81.1 (\pm 24.8)	0.60
Persistent candidemia	57 (32.4 %)	6 (54.5 %)	0.19
<i>C. albicans</i> (%) vs. non- <i>albicans</i>	86 (48.9 %)	5 (45.5 %)	0.99
Valvular prosthesis ^b	8 (4.5 %)	4 (36.4 %)	<0.01
Mitral prosthesis	6 (3.4 %)	2 (18.2 %)	0.07
Aortic prosthesis	3 (1.6 %)	2 (18.2 %)	0.03
Tricuspid prosthesis	1 (0.6 %)	0 (0 %)	1
Previous valve disease (prosthesis not included)	25 (15.9 %)	1 (14.3 %)	0.99
Pacemaker	2 (1.1 %)	0 (0 %)	0.99
In-hospital death	51 (29.0 %)	6 (54.5 %)	0.01
No persistent candidemia, prosthesis, pacemaker, or valve disease	81 (46.0 %)	8 (72.7 %)	0.08

^a Proportion of blood cultures that grew *Candida* among those drawn

^b One patient had both a mitral and a tricuspid prosthesis, and one patient had both a mitral and an aortic prosthesis

Multivariate analysis: valvular prosthesis $p < 0.01$ RR 13.7 (3.2–58)

in patients with candidemia who had neither persistent candidemia nor previous heart valve disease and were clinically unsuspected.

Several authors have underlined the role of clinical criteria and pretest probability in ruling out IE using echocardiography [6]. Unexplained bacteremia is considered to have a 5–40 % probability of being IE. The yield of routine echocardiogram in cases of BSI caused by *S. aureus* has been thoroughly studied [7–11], and current guidelines recommend that most patients with *S. aureus* bacteremia should be evaluated by echocardiography [2], even if they are classified as low risk [12], because the risk of endocarditis is as high as 13–22 % [11, 13].

CIE is an uncommon entity [14]. In their retrospective study, Nasser et al. suggested that patients with prosthetic heart valves who develop nosocomial candidemia are at notable risk of having or developing *Candida* prosthetic valve endocarditis months or years later [3]. To our knowledge, no previous studies have investigated prospectively the yield of echocardiography in candidemia.

Given the severity of and mortality associated with CIE, and the frequent delay of its diagnosis until significant vegetations or embolic complications are present, we consider that the prevalence of 11.5 % of cases of CIE among patients with candidemia studied with TEE is high enough to consider a recommendation for systematic echocardiography in this population. Considering the frequency of candidemia in our institution, this would only increase the workload of the echocardiography laboratory by less than four TEEs per month. Timely recognition enables better management and improved outcome in endocarditis [1, 15].

The only significant difference between patients with and without CIE was the presence of valvular prosthesis, which underlines the need to rule out CIE by TEE, especially in patients with a valvular prosthesis and candidemia. Except for this factor, we were not able to identify patients with a higher risk of IE.

In any case, the routine use of echocardiography confirmed three cases of CIE that would have gone undetected otherwise, because of the absence of valve disease, valvular prosthesis, or persistent candidemia. Atrial endocarditis, although uncommon, is well known [16–20], and in particular with *Candida* [21, 22]. As there were no clinical markers of CIE in this group, we recommend considering routine echocardiography for all patients with candidemia, including TEE when the TTE is not diagnostic of endocarditis, whenever the general situation of the patient allows it.

The limitations of our study are that, despite the intervention of the infectious diseases department, the number of patients with candidemia who did not undergo TEE was high, thus limiting the ability of the study to estimate the real prevalence of IE and introducing a possible selection bias. Although the recommendation was routine echocardiography, we found a significant difference between patients that underwent a TEE or not. TEE is not without risks, although serious complications are extremely rare, having been estimated at less than 1 in 5,000 [23]. Patients with candidemia are often too ill to undergo TEE, even when the approach is systematically recommended. Because of that, the actual incidence of CIE could be overestimated if there was a bias in performing TEE in some patients, which we cannot exclude. On the other hand, we cannot rule out the possibility that a diagnosis of CIE was missed because TEE was not performed systematically; therefore,

our data could underestimate the real incidence of CIE among patients with candidemia. Ours is a single-institution study and, accordingly, interpretation of the results requires caution.

Nevertheless, systematic TTE or TEE in patients with candidemia reveals a significant proportion of episodes of unsuspected endocarditis and should be offered to all patients with candidemia.

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Ana Fernández-Cruz had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Contribution of authors Ana Fernández-Cruz wrote the article and contributed to the design of the study, care of the patients, and collection of the data. Patricia Muñoz and Emilio Bouza contributed to the design of the study and care of the patients. Miguel Pedromingo contributed to the collection of the data. María Cruz Menárguez contributed to the collection of the data, maintenance of the database, and was the link with the echocardiography laboratory. Jorge Solís performed the echocardiography studies. Teresa Peláez and Marta Rodríguez-Créixems performed the laboratory work with fungal blood cultures. All the authors reviewed the manuscript.

Conflict of interest The authors declare no conflicts of interest involving this work.

References

1. Vos FJ, Bleeker-Rovers CP, Sturm PD, Krabbe PF, van Dijk AP, Oyen WJ, Kullberg BJ (2011) Endocarditis: effects of routine echocardiography during Gram-positive bacteraemia. *Neth J Med* 69(7): 335–340
2. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Müller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL; ESC Committee for Practice Guidelines (2009) Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new

- version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J* 30(19):2369–2413
3. Nasser RM, Melgar GR, Longworth DL, Gordon SM (1997) Incidence and risk of developing fungal prosthetic valve endocarditis after nosocomial candidemia. *Am J Med* 103(1):25–32
 4. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD; Infectious Diseases Society of America (2009) Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 48(5):503–535
 5. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR (2000) Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 30(4):633–638
 6. Chu VH, Bayer AS (2007) Use of echocardiography in the diagnosis and management of infective endocarditis. *Curr Infect Dis Rep* 9(4):283–290
 7. Cabell CH, Fowler VG Jr (2004) Importance of aggressive evaluation in patients with *Staphylococcus aureus* bacteremia. *Am Heart J* 147(3):379–380
 8. Fowler VG Jr, Li J, Corey GR, Boley J, Marr KA, Gopal AK, Kong LK, Gottlieb G, Donovan CL, Sexton DJ, Ryan T (1997) Role of echocardiography in evaluation of patients with *Staphylococcus aureus* bacteremia: experience in 103 patients. *J Am Coll Cardiol* 30(4):1072–1078
 9. Sullenberger AL, Avedissian LS, Kent SM (2005) Importance of transesophageal echocardiography in the evaluation of *Staphylococcus aureus* bacteremia. *J Heart Valve Dis* 14(1):23–28
 10. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB (2012) Predictors of mortality in *Staphylococcus aureus* bacteremia. *Clin Microbiol Rev* 25(2):362–386
 11. Rasmussen RV, Høst U, Arpi M, Hassager C, Johansen HK, Korup E, Schønheyder HC, Berning J, Gill S, Rosenvinge FS, Fowler VG Jr, Møller JE, Skov RL, Larsen CT, Hansen TF, Mard S, Smit J, Andersen PS, Bruun NE (2011) Prevalence of infective endocarditis in patients with *Staphylococcus aureus* bacteraemia: the value of screening with echocardiography. *Eur J Echocardiogr* 12(6):414–420
 12. Thangaroopan M, Choy JB (2005) Is transesophageal echocardiography overused in the diagnosis of infective endocarditis? *Am J Cardiol* 95(2):295–297
 13. Chang FY, MacDonald BB, Peacock JE Jr, Musher DM, Triplett P, Mylotte JM, O'Donnell A, Wagener MM, Yu VL (2003) A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. *Medicine (Baltimore)* 82(5):322–332
 14. Baddley JW, Benjamin DK Jr, Patel M, Miró J, Athan E, Barsic B, Bouza E, Clara L, Elliott T, Kanafani Z, Klein J, Lerakis S, Levine D, Spelman D, Rubinstein E, Tomos P, Morris AJ, Pappas P, Fowler VG Jr, Chu VH, Cabell C; International Collaboration on Endocarditis-Prospective Cohort Study Group (ICE-PCS) (2008) *Candida* infective endocarditis. *Eur J Clin Microbiol Infect Dis* 27(7):519–529
 15. Jenkins TC, Price CS, Sabel AL, Mehler PS, Burman WJ (2008) Impact of routine infectious diseases service consultation on the evaluation, management, and outcomes of *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 46(7):1000–1008
 16. Gutierrez-Fajardo P, Espinola-Zavaleta N, Romero-Cárdenas A, Reyes-Navarro L, Keirns C, Vargas Barron J (1998) Left atrial mural endocarditis: diagnosis by transesophageal echocardiography. *Echocardiography* 15(1):99–100
 17. Gray NA, Baddour LM (2002) Nonvalvular intravascular device-related infections. *Curr Infect Dis Rep* 4(4):293–298
 18. Grigorov V, Goldberg L, Manga P, Patel N (1999) Diagnosis and management of complicated left atrial mural endocarditis: the role of transesophageal echocardiography. *Echocardiography* 16(6):585–586
 19. Juang SE, Lai HC, Lan YC, Liu TJ, Lai HC (2005) Left atrial infective endocarditis with giant vegetation without involvement of the mitral valve—a case report of transesophageal echocardiography in diagnosis. *Acta Anaesthesiol Taiwan* 43(3):165–167
 20. Kearney RA, Eisen HJ, Wolf JE (1994) Nonvalvular infections of the cardiovascular system. *Ann Intern Med* 121(3):219–230
 21. Karabinos IK, Kokladi M, Katritsis D (2010) Fungal endocarditis of the superior vena cava: the role of transesophageal echocardiography. *Hellenic J Cardiol* 51(6):538–539
 22. Saba T, Günday M, Çiftçi Ö, Özülkü M, Erinanç H, Turan H, Çoban G (2013) An unusual case of *Candida* infection producing a fungus ball in the left atrial cavity. *Heart Surg Forum* 16(5):E276–E278
 23. Daniel WG, Erbel R, Kasper W, Visser CA, Engberding R, Sutherland GR, Grube E, Hanrath P, Maisch B, Dennig K, Schartl M, Kremer P, Angermann C, Iliceto S, Curtius JM, Mügge A (1991) Safety of transesophageal echocardiography. A multicenter survey of 10,419 examinations. *Circulation* 83(3):817–821