Инфекционные осложнения, связанные с имплантируемыми сердечными устройствами: диагностика, лечение и последние практические рекомендации

Алпизар Р.М.¹,
Флейшер Х.^{1, 2},
Рекс Л.³,
ХонШиделер К.⁴,
Орлов М.В.^{1, 5}

¹ Кафедра терапии, Медицинский центр Стюард Святой Елизаветы, Бостон, штат Массачусетс, США

² Кафедра терапии, отдел инфекционных заболеваний, медицинский центр Стюард Святой Елизаветы, Бостон, Массачусетс, США

³ Медицинская школа Университета Тафтс, Бостон, Массачусетс, США

⁴ Бостонский медицинский центр, отделение радиологии, Бостон, Массачусетс, США

⁵ Кафедра терапии, отдел кардиологии, секция электрофизиологии, Медицинский центр Стюард Святой Елизаветы, Бостон, Массачусетс, США

Кардиальные имплантируемые устройства (КИУ) широко распространены. Популяция с показаниями к КИУ продолжает увеличиваться и диверсифицироваться, что ведет к росту числа инфекций, связанных с КИУ. По мере развития технологий появляется все больше инструментальных методов диагностики. Тем не менее диагностика и лечение большинства инфекционных осложнений по-прежнему определяются клинической картиной, результатами посева крови и чреспищеводной эхокардиографии. В настоящий момент наиболее распространенными микроорганизмами, ответственными за эти осложнения, остаются стафилококки. При резистентных штаммах должны быть назначены антибиотики широкого спектра с сужением спектра через 72 ч, когда получены результаты посева. Отсутствие точных данных по микробиологии приводит к более длительным курсам лечения, а это в свою очередь влияет на качество жизни пациента, увеличивает стоимость лечения и повышает риск побочных эффектов. Раннее вовлечение и последующее наблюдение больных инфекционистами может уменьшить осложнения.

Контроль источника инфекции крайне важен для лечения, а культура/посев инфицированных компонентов КИУ поможет при выборе антибиотика и определении продолжительности лечения. Методы эксплантации КИУ будут зависеть от опыта специалиста и должны быть индивидуализированы в каждом конкретном случае. Технологии для эксплантации и имплантации КИУ продолжают развиваться в дополнение к новым устройствам, таким как кардиостимуляторы без электродов. Возможно, безэлектродные КИУ имеют низкий риск инфекционных осложнений, однако данные о микроорганизмах, подходящих методах лечения или методах экстракции для этих новых устройств ограничены.

Требования для реимплантации должны оцениваться для каждого конкретного случая, временная кардиостимуляция показана для пейсмекерозависимых пациентов.

В этой статье рассмотрены диагностика и лечение инфекций, связанных с КИУ, согласно действующим практическим рекомендациям.

Конфликт интересов. Профессор Михаил Орлов является реципиентом научного гранта от Boston Scientific и консультантом Abbott и Boston Scientific по темам, не связанным с предметом данной статьи.

Для цитирования: Алпизар Р.М., Флейшер Х., Рекс Л., ХонШиделер К., Орлов М.В. Инфекционные осложнения, связанные с имплантируемыми сердечными устройствами: диагностика, лечение и последние практические рекомендации // Инфекционные болезни: новости, мнения, обучение. 2020. Т. 9, № 3. С. 67–73. DOI: <https://doi.org/10.33029/2305-3496-2020-9-3-67-73> (англ.)

Статья поступила в редакцию 02.03.2020. Принята в печать 02.07.2020.

Infectious complications of implantable cardiac devices: diagnosis, management and current guidelines

Alpizar R.M.¹,

Fleisher J.^{1,2}, Rex L.³,

HonShideler C.⁴,

Orlov M.V.^{1,5}

¹ Department of Medicine Steward St. Elizabeth's Medical Center, Boston, Massachusetts

² Department of Medicine, Division of Infectious Diseases, Steward St. Elizabeth's Medical Center, Boston, Massachusetts

³ Tufts University School of Medicine, Boston, Massachusetts

⁴ Boston Medical Center, Division of Radiology, Boston, Massachusetts

⁵ Department of Medicine, Division of Cardiology, Section of Electrophysiology, Steward St. Elizabeth's Medical Center, Boston, Massachusetts

Cardiac Implantable Electronic Devices (CIED) are common in modern practice. The CIED-prescribed population continues to increase and diversify, which has led to a rise in CIED-related infections. As technology advances, more tools are available for diagnosis. However, diagnosis and treatment for most infections is still guided by clinical presentation, blood culture, and TEE. Currently, the most common organism continues to be the *Staphylococcus* species. Resistant variants should be covered empirically and narrowed after 72 hours when cultures develop. Lack of accurate microbiology data results in longer courses of treatment, which affects the patient's quality of life, increases the cost, and has greater risk for side effects. Early involvement and follow-up with infectious diseases specialists may help to minimize complications.

Source control is imperative for treating the infection, and culturing of the infected hardware, will help to determine the choice and duration of antibiotic therapy. Extraction techniques for CIED systems will depend on the expertise of the specialist and should be individualized case-by-case. New techniques for extraction and implantation continue to emerge, in addition to new devices such as leadless pacemakers. These may have reduced risk of infection, however, data on infectious organisms, appropriate treatments, or extraction techniques for these new devices are limited.

Requirements for re-implantation should be evaluated for every case and temporary pacing is a viable option for patients who are pacemaker-dependent.

In this article, we will review the diagnosis and management of CIED-related infections as stated by current guidelines.

Conflict of interest. Dr. Michael Orlov has received a research grant from Boston Scientific, and is a consultant to Abbott and Boston Scientific, unrelated to the subject of this article.

For citation: Alpizar R.M., Fleisher J., Rex L., HonShideler C., Orlov M.V. Infectious complications of implantable cardiac devices: diagnosis, management and current guidelines. *Infektsionnye bolezni: novosti, mneniya, obucheniye* [Infectious Diseases: News, Opinions, Training]. 2020; 9 (3): 67–73. DOI: <https://doi.org/10.33029/2305-3496-2020-9-3-67-73>

Received 02.03.2020. **Accepted** 02.07.2020.

Introduction

Cardiovascular implantable electronic devices (CIED) are a life-saving therapy that have been used with increasing frequency over the past several decades. There were 4.2 million primary implantations of CIEDs in United States between 1993 and 2008 alone [1]. The European Society of Cardiology reported that the Russian Federation had 140 centers capable of implanting CIEDs and 34,758 devices were implanted in the year of 2013 [2]. The types of CIEDs found in this guidelines included Permanent pacemakers (PPM), Implantable Cardioverter Defibrillators (ICD) and Cardiac Resynchronizing Therapy (CRT). With the expansion in indications for CIEDs and the increasing life expectancy of the population the prevalence of patients with CIEDs will continue to grow. The techniques for implanting and extracting these devices continue to develop and have become more minimally invasive but the infection-related complications have significantly increased [1, 2]. CIED-

related infections continue to represent an important and increasing burden on the medical system, even as they have definitely improved patient's quality of life. A U.S. report from 2011 stated that the cost of treatment for one CIED infection ranged between \$28,676 and \$53,349 [1]. More recent reports from European studies estimate costs between \$34,894 to \$65,832 in Germany and a mean cost of \$40,421 in UK [3, 4]. In this article, we will review the diagnosis and management of CIED-related infections.

Diagnosis

Definitions

The subtypes of CIED infections vary between different society guidelines. The 2015 European Society of Cardiology guidelines divide CIED infections into two main types: local device infection and cardiac device-related infective endocarditis [5]. This division acts to categorize the infection as either

an intravascular or soft tissue infection. The 2017 American guidelines classify CIED infections into more specific subtypes: isolated generator pocket infection with and without bacteremia, isolated pocket erosion, occult bacteremia with probable CIED infection, lead infection, and pocket site infection with endocarditis or lead involvement [6]. These definitions help guide diagnostic workup and treatment.

Initial presentation and diagnostic work-up

The majority of CIED-related infections with local device involvement most commonly present in the weeks to months following implantation [7]. Symptoms of pocket infection are diverse, ranging from soft tissue infection characterized by signs of inflammation (erythema, pain, increased temperature and increased volume of the area) [8], to more severe presentations such as erosion (figure 1) with exposure of hardware (generator or leads), ulceration, and systemic involvement from fevers to full blown septic shock. Patients with erosion resulting in exposure of the leads or generator are considered to be infected regardless of the presence of local or systemic symptoms, as this puts the hardware in direct contact with skin bacteria [5].

Many patients initially present with clinical findings suggestive of an exclusively local device infection, but further diagnostic workup may reveal a more extensive intravascular involvement. One study showed positive lead culture in 72% of patients with local device infection. In another study, of 241 patients with pocket infection who underwent transesophageal echo, 26 patients had vegetations detected on image [9]. The American guidelines reported that lead vegetations were present on transesophageal echocardiogram (TEE) (figure 2) in 88% of patients who appeared to have only a local device infection [7]. More recent data show lead involvement in over 40% of patients that initially were diagnosed with local device infection. Other studies estimate a higher incidence of lead involvement accounting for the fact that TEE is sometimes not performed [8]. These data emphasize the importance of appropriate imaging and blood cultures as the standard diagnostic work-up for every patient presenting with findings suggestive of localized or systemic CIED infection. Furthermore, differentiating between local device infection and intravascular CIED infection cannot be done without both blood cultures and TEE.

Two sets of blood cultures should be drawn before starting any antibiotic therapy [6]. If antibiotic therapy is started before getting blood cultures, diagnostic workup should be continued as if the blood cultures were positive. If the blood cultures are positive or there is high suspicion for systemic infection (high fevers, hemodynamic instability, and risk factors), cardiac valves and leads should be evaluated by TEE [8]. Transthoracic echocardiogram (TTE) should not be considered standard of care in this setting as its sensitivity only ranges between 24–32% [9].

When there is an unclear diagnosis, other imaging modalities have been studied and could potentially be useful in aiding with the diagnosis. PET/CT (positron emission tomography/computed tomography) has been shown to have a sensitivity of 87% and specificity of 100% in local pocket infec-

tions [10]. Nuclear medicine white blood cell scan has a higher sensitivity of 94% [11], but two days are required to perform the study, thus making PET/CT often a more practical imaging modality. Except for the cost that could be prohibitive in some areas.

If pocket infection is confirmed, performing a TEE is recommended in order to guide the length of treatment required [5, 6].

For patients with persistent bacteremia without evidence of CIED infection, as proven by a negative TEE and no signs of pocket infection, alternative sources of bacteremia should be assessed. As long as the patient remains bacteremic IV therapy has so far been the only proven effective therapy. If there is no clear source, CIED seeding should be considered [6].

When removing a device, swab culture of the pocket has been shown to grow organisms in 31–44.2% of the cases, while tissue culture from the pocket has grown organisms in 52.9–69% of the cases. Hardware culture (such as battery, connector and leads) have the highest sensitivity with 63.9–90% showing growth, even when antibiotics have been started [12]. New technology has improved the chances of getting new cultures and if possible, should be used [20].

Epidemiology

Knowing which microbes are the most common is crucial to choosing the initial therapy. According to the European and American guidelines, *Staphylococcus aureus* and coagulase-negative *Staphylococcus* (CoNS) are the most frequent microbes to cause infection (60–80%). *Staphylococcus aureus* presents more commonly in systemic infections (half of which are MRSA), while CoNS are more frequent in local device infections (Table), and the rate of methicillin-resistant CoNS is variable depending on the association with health care environments [12].

Staphylococcus aureus alone has been associated with a longer duration of bacteremia, which can lead to longer hospitalization and increased mortality [14]. The most common

Figure 1. A photograph demonstrates an erosion of an ICD generator through the skin. Centimeter scale is shown on top

Figure 2. TEE Images of different vegetations on implanted leads (white arrow)

gram-positive bacteria after *Staphylococcus aureus* are enterococcus and streptococcus, although the sample size that reports this prevalence is small [12]. Gram-negative bacteria are responsible for less than 10% of CIED infections, of which *Klebsiella pneumoniae* and *Serratia marcescens* are the most common [14]. *Pseudomonas* species do not commonly cause CIED-related infections. Additionally, fungal infections have been described in only 0.9–2% of CIED infections [12, 14].

Management

Microbiology data is crucial to determine the appropriate choice of antibiotic and therapy duration.

The type of microbe dictates not only the antibiotic choice, but also the length of treatment and the need for device extraction. For example, extraction is almost always needed in *Staphylococcus* infections as they are able to form a biofilm which prevents the antibiotic therapy alone from clearing the infection in any device [15].

A multidisciplinary team that includes Infectious diseases should be involved early in the course. Initial antibiotic management should start after blood cultures have been drawn. If antimicrobial therapy is started before blood cultures are drawn, microbial growth in the blood cultures may be affected and that may lead to longer courses of broad antibiotic coverage which when unnecessary may affect the patient's quality of

Incidence and sensitivity of Microbial CIED infections

Organism	Overall incidence, %	Incidence of systemic infection in the first year, %	Incidence of systemic infection after a year of insertion, %	Incidence of isolated pocket infection in the first year of insertion, %	Incidence of isolated pocket infection after a year of insertion, %
Staphylococcus	60–80	51.7	44.5	30.2	16.3
MSSA	15.8	36.8	30.8	40.5	35.4
MRSA	15	42.5	39.8	29.8	34.4
CoNS	37.6–42	27.6	26.1	40	53.6
Non Staph Gram positive	6.7	5.7	8.1	0.5	0.0
VSE	2.8	–	–	–	–
VRE	1.4	–	–	–	–
Streptococci	2.5	–	–	–	–
Gram negative	6.1–9.1	–	–	–	–
Fungal	0.9–2	–	–	–	–

Note. MSSA – methicillin-sensitive *Staphylococcus aureus*, MRSA – methicillin-resistant *Staphylococcus aureus*, CoNS – coagulase-negative staphylococci, VSE – vancomycin sensitive enterococci, VRE – vancomycin resistant enterococci [1, 5, 12, 13].

life, increases economical burden and risk potential life threatening side effects. However, antibiotic treatment should not be delayed in unstable patients when blood cultures cannot be readily drawn [5].

Choice of antibiotic will depend on the pathogen and the extent of the infection [13]. Patients with findings suspicious for systemic infection should be started on broad-spectrum intravenous coverage for gram-positive organisms including MRSA and gram-negative organisms excluding *Pseudomonas* [13]. In the US Vancomycin is the first choice for *Staphylococcus* species coverage, starting with a loading dose that should be based on weight and creatinine clearance. The maintenance dose of 30 to 60 mg/kg in day divided in 2–3 doses should be adjusted with vancomycin trough ideally with the help of pharmacy in order to optimize therapy, new recommendation focus on working with area under the curve instead of troughs.

Gram-negative coverage will vary depending on each hospital susceptibility data, but multiple European guidelines recommend a third generation cephalosporin [5, 13].

Once the initial diagnostic workup has been done to identify whether the infection is limited or systemic, as well as the species of the pathogen involved, antibiotic treatment should be narrowed to the correct microbe and sensitivity.

If there is evidence of a valve vegetation, antibiotic treatment should last for four weeks in patients with native valves and for six weeks in those with prosthetic valves or native valves with staphylococcal endocarditis [5, 6, 13]. If there is a lead vegetation without the valve involvement, antibiotic treatment of *Staphylococcus* infection should last four weeks and two weeks for any other bacteria. In all cases, the length of treatment should be counted from the day of CIED and leads removal (figure 2, 3) or clearance of blood cultures depending on which event happened later [5, 6, 13].

For patients with signs of generator infection with negative TEE, the decision to remove the CIED should be made depending on microbiology data, such as whether the bacteria produce biofilm. Choice of antibiotic should be directed to sensitivity results and continued for two weeks [5, 6, 13].

If there is early superficial inflammation within thirty days of implantation, the clinician can decide to simply observe or to begin a seven to ten day course of oral antibiotics with staphylococcus coverage [5]. If pocket infection is confirmed and blood cultures are negative, antibiotics should be directed to culture and sensitivity from pocket cultures [6]. If cultures are negative consider covering skin flora, streptococci and staphylococci mainly staphylococci CoNS. If antibiotics were started cultures may be affected, but resistant organisms such as *pseudomonas* and MRSA would not require covering as they would grow even after initiation of most antibiotics.

Patients should follow up with an infectious diseases specialist before completing their antibiotic course in order to determine the need for a longer course or a change of antibiotics.

Indications for extraction

Regardless of microbiology data, generator and lead extraction should be done within three days of diagnosing a pocket abscess, erosion with exposure of any component of the CIED, lead vegetation, or endocarditis [15]. Inadequate source con-

trol via failure to remove all parts of a CIED leads to seven times the risk for mortality compared to the risk of mortality when removing the whole CIED system [15].

The decision to remove a CIED in the setting of bacteremia alone with a negative TEE depends on the culture data. The presence of only one positive culture (not MRSA) does not usually indicate that CIED removal is necessary. If there is evidence of systemic involvement or more than one positive culture, the CIED should be removed in the presence of the following microbes: *Staphylococcus aureus*, coagulase negative *Staphylococcus*, *Propionibacterium* species, or *Candida* [5, 6, 13]. When there is infection with *Enterococcus*, or Alpha- and Beta-hemolytic streptococcus, CIED removal should be considered in patients with low risk of procedure complications [6]. If the risk associated with removal appears to be high when evaluated by a clinician trained in CIED removal, observation and medical management by an infectious diseases specialist with antibiotic-directed therapy is appropriate [6, 13]. If bacteremia persists or recurs after completion of antibiotic treatment, the CIED should be removed. When bacteremia is caused by Gram negative or *Pneumococci bacteria*, the CIED should also be removed if there is reappearance of bacteremia after completion of antibiotic treatment [6, 13].

If the patient's life expectancy is less than one year and the risk of extraction is high, antibiotic treatment followed by suppression therapy without extraction may be considered [16]. When there is superficial infection that does not invade fascia or muscle after surgical exploration, there is no indication for removal, but the patient should be reevaluated after completing antibiotic treatment.

Lead Extraction Techniques

Since the leads are intravascular and in contact with the endocardium, removal of cardiac leads is more complex and requires more preparation than a generator extraction. The technique will depend on multiple variables (patient, type of lead, and center experience/availability of specialized technology). The procedure might be done under sedation or general anesthesia depending on the complexity of the case, and a multidisciplinary approach with surgical consultation is advised in order to avoid major complications [6, 13].

Direct traction: This technique is more successful for Iso-diametric leads indwelling less than a year after implantation. Manual traction is used to remove the lead assisted by stylets, which can either interlock with the lead or simply provide more stability.

Figure 3. Explanted defibrillator lead demonstrates a vegetation (arrow). Centimeter scale is shown at the bottom

Figure 4. Surgical removal of an implanted lead and vegetation (arrow), view through the right atrial incision

Telescoping sheaths are an option designed to dissect the lead from any epithelized tissue by extending over the lead.

Excimer Laser sheaths or mechanical rotational cutting sheaths are used to free and extract longer indwelling leads that are surrounded by more extensive fibrous tissue and adhesions [17].

When minimally invasive techniques are unsuccessful or the vegetation is greater than 2cm, surgical removal is advised (figure 4) to avoid vascular tear or vegetation embolization to the lungs [13].

Re-implantation

Before proceeding with re-implantation of a CIED, the patient should be re-assessed for the continued need of CIED [5, 6, 13]. In patients who have achieved appropriate source control, with clear blood cultures for 72 hours and no other source of infection such as peripheral abscesses, re-implantation may be performed [6, 13, 14]. Traditionally, the side of implantation is switched in patients with intravascular infections, as using the same access has been associated with a high risk for reinfection, but recent data has shown that an ipsilateral lower thoracic implantation technique for patients with limited access options, unavailable contralateral pectoral site and patent axillary vein can be performed with no reinfection [18]. This may be an alternative approach to a surgical epicardial or a femoral pacing system with a mean of 10 days between the extraction and re-implantation. Temporal pacing may be provided in the interim via an active-fixation pacing lead introduced through the internal jugular vein or subclavian vein [18].

In patients with an isolated pocket infection, re-implantation may be performed on a different side after a full extraction of the original system. Some studies have suggested that re-implantation may be safely done within 24 hours of extraction, as long as there is no evidence of intravascular contamination [19].

Pacemaker dependence is not a contraindication or a reason to delay extraction. Temporary pacing leads may be used in the interim after extraction while planning and evaluating for a new, permanent device. In addition, leadless pacemakers are a novel option, which is being increasingly used for pacing following the extraction [18].

ДЛЯ КОРРЕСПОНДЕНЦИИ

Орлов Михаил В. (Michael V. Orlov) – MD, PhD, Steward St. Elizabeth's Medical Center, 736 Cambridge Street, Boston, MA 02135
E-mail: Michael.Orlov@steward.org

ЛИТЕРАТУРА/REFERENCES

1. Greenspon A.J., et al. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States. *J Am Coll Cardiol.* 2011; 58: 1001–6.
2. Raatikainen M.J.P., et al. Statistics on the use of cardiac electronic devices and electrophysiological procedures in the European Society of Cardiology countries: 2014 report from the European Heart Rhythm Association. *Europace.* 2015; 17: i1–75.
3. Ahsan S.Y., et al. A simple infection-control protocol to reduce serious cardiac device infections. *Europace.* 2014; 16: 1482–9.
4. Sohail M.R. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med.* 2011; 171: 1821.
5. Habib G., et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J.* 2015; 36: 3075–128.
6. Kusumoto F.M., et al. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. *Heart Rhythm.* 2017; 14: e503–51.
7. Klug D., et al. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation.* 2007; 116: 1349–55.
8. Tarakji K.G., et al. Cardiac implantable electronic device infections: presentation, management, and patient outcomes. *Heart Rhythm.* 2010; 7: 1043–7.
9. Sekar P., et al. Comparative sensitivity of transthoracic and transesophageal echocardiography in diagnosis of infective endocarditis among veterans with *Staphylococcus aureus* bacteremia. *Open Forum Infect. Dis.* 2017; 4: ofx035.
10. Sarrazin J.-F., et al. Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. *J Am Coll Cardiol.* 2012; 59: 1616–25.
11. Erba P.A., et al. Radiolabeled WBC scintigraphy in the diagnostic workup of patients with suspected device-related infections. *JACC Cardiovasc Imaging.* 2013; 6: 1075–86.
12. Hussein A.A., et al. Microbiology of cardiac implantable electronic device infections. *JACC Clin Electrophysiol.* 2016; 2: 498–505.
13. Blomström-Lundqvist C., et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections – endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European

Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). EP Europace. 2019; 2019: euz246. DOI: <https://doi.org/10.1093/europace/euz246>

14. Sohail M.R., et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. J Am Coll Cardiol. 2007; 49: 1851–9.

15. Peacock J.E., et al. Attempted salvage of infected cardiovascular implantable electronic devices: are there clinical factors that predict success? Pacing Clin Electrophysiol. 2018; 41: 524–31.

16. Tan E.M., et al. Outcomes in patients with cardiovascular implantable electronic device infection managed with chronic antibiotic suppression. Clin Infect Dis. 2017; 64: 1516–21.

17. Hasumi E., et al. Novel extraction technique of retained pacemaker and defibrillator lead during heart transplantation. PLoS One. 2018; 13: e0203172.

18. Liang J.J., et al. Low lateral thoracic site for cardiac implantable electronic device implantation: a viable alternative in patients with limited access options after infected device extraction. Heart Rhythm. 2017; 14: 1506–14.

19. Mountantonakis S.E., Tschabrunn C.M., Deyell M.W., Cooper J.M. Same-day contralateral implantation of a permanent device after lead extraction for isolated pocket infection. Europace. 2014; 16: 252–7.

20. Portillo M.E., Salvadó M., Trampuz A., Siverio A., Alíer A., Sorli L., et al. Improved diagnosis of orthopedic implant-associated infection by inoculation of sonication fluid into blood culture bottles. J Clin Microbiol. 2015; 53 (5): 1622–7.