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INFECTIOUS ENDOCARDITIS CAUSED BY A RARE AGENT BURKHOLDERIA CEPACIAN

Abstract

Introduction. Infective endocarditis (IE) caused by Burkholderia cepacia is a very rare and poorly characterized form of endocarditis. **Material and methods.** We observed a case of delayed prosthetic mitral valve IE caused by Burkholderia cepacia in a 34-year-old patient. **Results.** A patient with a congenital ventricular septal defect underwent cardiac surgery three times in the past, including the removal of vegetations due to IE at the age of 17 and the mitral valve plasty in association with the plastic re-repair of ventricular septal defect at the age of 33. The last was complicated by postoperative pyogenic sterno-mediastinitis, thoracomyoplasty was performed. Ten months later the fever with chills appeared again, a large vegetation on a mitral valve prosthesis was revealed, and Burkholderia cepacia bacteremia with multidrug resistance to antibiotics was found. After the start of treatment with trimethoprim/sulfamethoxazole, normal body temperature was observed, but the course of IE was complicated by thromboembolism with a fatal outcome. **Conclusions.** Multidrug resistance of the pathogen to antibiotics, including those empirically prescribed for IE treatment, is the main risk factor for a poor clinical outcome of IE caused by Burkholderia cepacia. The lack of generally accepted recommendations on antibiotics dosing, prescribed in accordance with the microorganism sensitivity, contributes to the problem of IE caused by Burkholderia cepacia management.

Key words: *Infective endocarditis, endocarditis of the valve prosthesis, Burkholderia Cepacia*

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VSD — ventricular septal defect, IE — infective endocarditis

According to the latest estimates 79.3–88% of infective endocarditis (IE) cases are caused by gram-positive cocci — staphylococci, streptococci or enterococci, and only in 5% of cases the disease is caused by gram-negative bacteria [1–6], and specifically by the HACEK group gram-negative bacteria (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, Kingella) [7,8] in 1.4–3% of cases, and by gram-negative bacteria not belonging to the HACEK group (Escherichia coli, Pseudomonas aeruginosa, Serratia, Acinetobacter, etc.) in approximately 2% of cases [4, 9]. ICE-PCS international cohort study has shown that IE caused by the gram-negative bacteria not belonging to the HACEK group was associated with medical interventions in 57% of cases and also characterized by high mortality (24%) despite frequent surgical treatment (51%) [4].

Gram-negative aerobic bacteria Burkholderia cepacia (formerly named as Pseudamonas cepacia) constitute a group of low-virulent opportunistic pathogens, which are ubiquitous in the environment (below ground, in water, and in agricultural crops) that are capable of causing severe

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pneumonia in patients suffering from cystic fibrosis [10]. Burkholderia cepacia bacteria are very rare infective agents of IE [11, 12]. The most important characteristic of Burkholderia cepacia is its natural multi-drug resistance to antibiotics and disinfectants. The bacteria can persist in phagocytes, form biofilms, have a wide range of adhesion factors, and are capable of colonizing the endocardium, valve prostheses and catheters surface [9, 13, 14]. The literature shows about 50 IE cases caused by Burkholderia cepacia, most of which are endocarditis of injection drug users cases as well as prosthetic endocarditis or endocarditis in patients with immunodeficiency [9, 11, 12, 15, 16]. We have observed the case of prosthetic mitral valve IE caused by Burkholderia cepacia.

Female patient C., 34 years old, hospitalized with complaints of shaking chills, fever up to 39.0 °C, dry cough, and asthenia. The patient has a history of congenital heart disease: at the age of 3, she underwent the pulmonary artery banding for ventricular septal defect (VSD) with high pulmonary hypertension. At the age of 17, the patient suffered an infective endocarditis on the mitral valve, requiring the following surgical correction: removal of vegetations in association with the plastic repair of ventricular septal and pulmonary artery. At the age of 27 (2009) she completed a pregnancy without complications. The baby was timely delivered. In January 2015, though she was in satisfactory condition, the recanalization of the ventricular septal defect and 3rd degree mitral regurgitation were revealed during the echocardiography procedure. In March 2015, the mitral valve plasty with Sorin No. 29 prosthesis and VSD plasty using the synthetic patch made of dacron were carried out with preservation of the subvalvular structures of the posterior mitral leaflet. The late postoperative period was complicated by pyogenic infection of the post-operative wound with the development of fistulous form of chronic sternomediastinitis. In October 2015, the partial removal of presternum and mesosternum was carried out, and in January 2016, thoracomyoplasty of the thorax anterior wall wound with local tissues was performed. The patient continuously took warfarin (INR 2.5–3.5).
Current deterioration in the condition was noted on November 10, 2016, when with no apparent cause the patient developed subfebrile fever, and 2 days later the patient experienced febrile fever up to 38.5 °C with chills. In addition, on November 14, 2016, the patient noted a short term pain on the right of her lower back, accompanied by darkened urine. The patient took levofloxacin on an outpatient basis without any improvement. Dry cough started on November 18, 2016. On November 20, 2016, the temperature increased to 39.0 °C. The patient was urgently hospitalized with suspected pneumonia.
On admission, the patient's condition was assessed as moderate. The patient was conscious, cooperative. Body temperature was 38.5 °C. Regional lymph nodes were not palpable. Peripheral edema and cyanosis were not noted. Joints were not externally changed. The thorax was symmetrical. There was a postoperative scar without infiltrative changes on the anterior thoracic wall along the median line. Respiratory rate was 16 breaths per minute. Breathing was vesicular. There were muted small bubbling rales in the lower parts of the thorax on both sides. The heart rhythm was regular. Heart sounds were muffled, and there was a holosystolic murmur, best heard at the apex and radiated to the axilla, at all auscultation points. Heart rate was 90 bpm, and blood pressure was 110/70 mm Hg. Abdomen was soft and nontender. The liver did not protrude below the costal margin. The lower pole of the spleen was palpable. Urination was normal. Stool was regular and formed.
The complete blood count of 11/21/2016 showed: leukocytes $22.1*10^9$/l, erythrocytes $3.27*10^{12}$/l, hemoglobin 91 g/l, platelets $180*10^9$/l, banded neutrophils: 2%, segmented neutrophils 75%, lymphocytes 12%, monocytes 1%, ESR 76 mm/h. The urinanalysis of 11/21/2016 showed: relative density 1.018, no protein, epithelial cells 1–2 per HPF, leukocytes 2–4 per HPF, and erythrocytes 0–1 per HPF. There was no growth in urine culture from 11/21/2016. Biochemical analysis from 11/21/2016 showed: creatinine 61.2 μmol/l, ALT 21 IU/l, AST 24 IU/l, C-reactive protein 279.2 mg/l; INR 3.62. Venous hypertension was revealed and no focal infiltrative changes were observed on the chest X-ray 11/20/2016. Abdominal and retroperitoneal ultrasound showed: diffuse changes in pancreas, splenomegaly; no kidney pathology was revealed. EGD showed duodenogastric reflux.

Transthoracic (11/22/2016) and transesophageal (11/25/2016) Echo revealed mitral valve prosthesis without functional abnormalities, 1st degree mitral regurgitation, suspicion of vegetation or thrombus on the prosthesis (floating formation 0.9 × 1.2 cm) (Figure 1). Ceftriaxone 2 g intramuscularly (single dose) was initially prescribed in connection with the suspected pneumonia and was ineffective: sustained febrile fever up to 39 °C with chills and intoxication persisted.

In relation with the identification of floating formation of the mitral valve and 3-week sustained fever above 38 °C that could not be explained by any other reasons, on the fifth day of hospital treatment in accordance with the diagnostic criteria of the European Society of Cardiology, 2015 [17], IE of the prosthetic mitral valve was suspected in the patient with predisposing heart disease. Taking into account the latest recommendations for the empirical treatment of the prosthetic valve IE associated with prior medical care, triple-antibiotic combination of vancomycin 1.0 g b.i.d. IV infusion, gentamycin 80 mg b.i.d. intramuscularly, and rifampicin 0.3 g t.i.d. orally was prescribed [17]. However, on treatment, fever held up for 5 days with daily rises up to 39–39.5 °C and shaking chills. The blood test revealed persistent leukocytosis and decreased hemoglobin to 78 g/l. Transthoracic Echo from 11/29/2016: the floating formation of the unchanged size remained on the mitral valve prosthesis with no signs of dysfunction of the prosthesis.

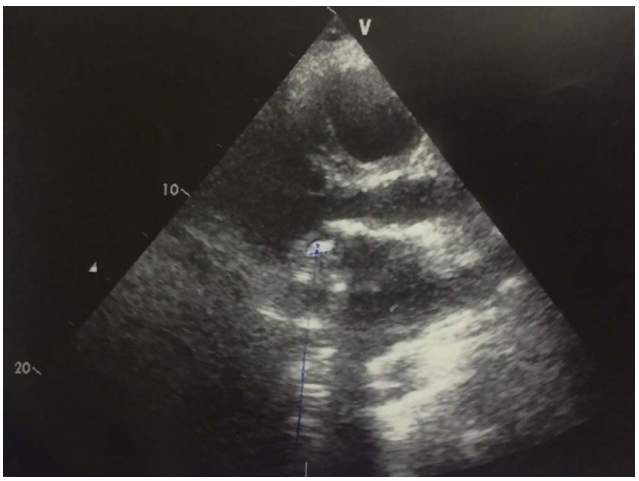

Figure 1. *Transthoracic echocardiogram of patient C.: a floating vegetation (0.9 × 1.2 cm) on a prosthetic mitral valve*

On November 29, 2016, the results of a microbiological blood test from 11/22/2016 were obtained. In three separate blood cultures taken at an interval of more than 1 hour, the growth of gram-negative microorganism Burkholderia cepacia resistant to azlocillin, amoxicillin / clavulanic acid, gentamycin, levofloxacin, doxycycline, imipenem/cilastatin, ceftriaxone, meropenem, nitrofurantoin, cefepime, piperacillin/tazobactam, linezolid and sensitive only to bacteriostatic agent chloramphenicol, which is not recommended for long-term treatment of IE. Therefore, according to available literature data on the sensitivity of Burkholderia cepacia to co-trimoxazole and the greatest effectiveness of treatment of IE caused by Burkholderia cepacia with co-trimoxazole IV at doses corresponding to 4–15 mg/kg of trimethoprim and 20–75 mg/kg of sulfamethoxazole [12, 15], starting on November 30, 2016, co-trimoxazole 960 mg t.i.d. IV was assigned, while the other antibiotics were canceled. In accordance with the presence of a major diagnostic criterion (mitral valve vegetation) and three minor criteria (predisposing heart disease, fever > 38 °C, positive blood culture that do not correspond to a major bacteriological criterion) that are required for definite diagnosis of IE, the principal diagnosis was: secondary acute IE of a prosthetic mitral valve, CHD–VSD, history of Infective endocarditis in 1999, surgical closure of ventricular septal defect in 2015, Sorin mechanical mitral valve prosthesis, secondary anemia; CHF NYHA 2 class. On November 30, 2016, the patient was consulted by a cardiac surgeon, taking into account the technical difficulties of repeated cardiosurgical intervention and the absence of dysfunction of the prosthesis, despite the presence of risk factors for thromboembolic complications (vegetation larger than 10 mm and suspicion of the history of thromboembolism of the right renal artery), it was recommended to continue antibiotic therapy.

On the second day of therapy with co-trimoxazole, the patient's condition improved significantly: the temperature did not exceed 37 °C, chills stopped, weakness decreased, and appetite and well-being improved. On the fifth day the temperature returned to normal. However, on December 7, 2016, the patient experienced a sharply painful Osler's node, a typical IE manifestation caused by embolism of the arterioles of the fingers pads

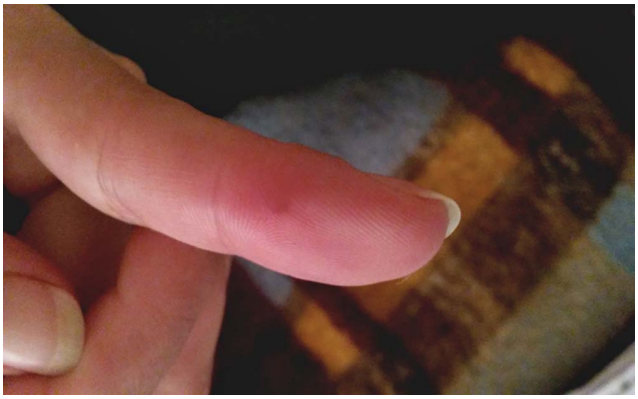

Figure 2. *Osler's node on the finger of a patient C.*

(Figure 2), and on December 08, 2016, an acute cerebrovascular accident in the right hemisphere with hemorrhagic transformation occurred, which led to the patient's death 3 days later.

Discussion

IE caused by Burkholderia cepacia was described more than 50 years ago [15, 18]. Based on literature data and our clinical observation, IE caused by this rare pathogen is most likely to occur on prosthetic heart valves and intracardiac devices or in patients with immunodeficiency and in injection drug users [9, 11, 16, 19]. However, it may also occur on natural valves in the absence of any special epidemiological situations [20]. In recent years, the association of Burkholderia cepacia infection, including the development of bacteremia or IE, with in-hospital medical care, especially with the insertion of intravenous catheters, permanent pacemakers, hemodialysis, and prosthetic heart valves has increasingly been reported [21–24]. Shilpa Bhojraj et al. described two cases of prosthetic IE caused by Burkholderia cepacia with a probable common source of nosocomial infection [16]. Although the probability of transmission of this infection "from patient to patient" in cystic fibrosis is recognized [10], the mechanisms of infection with Burkholderia cepacia with the development of IE have not been sufficiently studied.

In the clinical situation that we observed, the ineffectiveness of the conventional starting empirical therapy for IE of the prosthetic valve with a combination of rifampicin, vancomycin, and gentamycin, which are prescribed according to ESC recommendations based on the highest likelihood of infection with Gram-positive cocci [17], indirectly indicated a possible atypical pathogen. Though there were no premises for assuming infection with Burkholderia cepacia before blood culture results.

The main problem in the treatment of infections caused by Burkholderia cepacia is a high level of resistance to most antibiotics, including antibiotics commonly used in the treatment of IE [25]. Molecular mechanisms of resistance of the microorganism include efflux pumps for chloramphenicol, porin proteins for aminoglycosides, as well as beta-lactamases and antibiotic-binding proteins for a wide variety of antibiotics, including rifampicin [13, 14, 18]. The causative agent is most sensitive to ticarcillin, carbapenem (meropenem), cephalosporins (ceftazidime, cefepime), fluoroquinolones (levofloxacin), piperacillin [25, 26, 27]; however, in our case, in vitro resistance was detected. According to the literature, the causative agent is also sensitive to trimethoprim-sulfamethoxazole [18, 25, 26]. Treatment with this drug is considered to be the most effective for treating IE caused by Burkholderia cepacia [15, 20]. The sensitivity to co-trimoxazole in vitro was not tested in the case of IE. However, clinically there was a normalization of temperature and improvement of the patient's condition in 5 days after initiation of co-trimoxazole therapy.

Due to the rarity of the disease, there are no recommendations for the antibacterial therapy of IE caused by Burkholderia cepacia. The decision of which antibiotic is chosen should be based on the results of determining the sensitivity of the isolated pathogen and literature data on the effectiveness of its use in cases of IE [28]. Burkholderia cepacia strains isolated from patients with IE are, according to the literature, most often sensitive to trimethoprim-sulfamethoxazole and chloramphenicol, and in most cases antibacterial therapy without co-trimoxazole was ineffective [12]. In cases described in the literature, trimethoprim-sulfamethoxazole was administered at doses ranging from 960 to 8,400 mg/day intravenously as a monotherapy or in combination with kanamycin and/or polymyxin B for a period ranging from 10 days to more than 10 months [12, 15, 18, 29]. The use of meropenem, ceftazidime (as well as their combination), levofloxacin, piperacillin-tazobactam [12, 20] has also been described. Taking into account the high incidence

of relapse in the treatment of IE caused by Burkholderia cepacia, the duration of antibiotic therapy is no less than 8–10 weeks followed by regular follow-up of the patient for 6–12 months [12, 18].

The analysis of cases of IE caused by Burkholderia cepacia that is presented in the literature indicates an improvement in the prognosis with a combination of antimicrobial therapy with cardiac surgery, which is performed in approximately half of patients [15]. Nevertheless, in more than 50% of the observations of IE caused by this rare pathogen the patient died.

Unfortunately, in the observed patient, in addition to the rare causative agent that is resistant to most antibiotics for the treatment of IE, a high risk of thromboembolic complications was initially identified and according to current recommendations, despite the preservation of the function of the valve prosthesis, there were indications for surgical treatment. However, this procedure had to be avoided because of the technical difficulties associated with repeated surgery on the heart [17, 30]. It is possible to decrease the risk of thromboembolism with IE by applying 2–3 weeks of effective antibacterial therapy [31]. However, on the 9th day of treatment with co-trimaxazole, the patient suffered an ischemic stroke with hemorrhagic transformation, which led to death.

Conclusion

IE caused by Burkholderia cepacia is a rare and inadequately studied form of the disease with a relatively unfavorable prognosis due to the multidrug resistance of the pathogen to antibiotics that are empirically prescribed for IE, the tendency of infection to relapse, and the tendency of the disease to most frequently relapse in patients with prosthetic heart valves. The treatment of IE caused by Burkholderia cepacia is complicated by the lack of generally accepted recommendations determining the necessary doses of antibiotics, which should be prescribed in accordance with the sensitivity of the identified causative agent. The duration of antibiotic therapy for IE caused by Burkholderia cepacia is also still a matter of discussion. Our observation illustrates the need for bacteriological verification of the IE diagnosis, especially in cases of resistance to standard empirical treatment.

Conflict of interests

The authors declare no conflict of interests.

References

1. Munoz P., Kestler M., De Alarcon A. et al. Current Epidemiology and Outcome of Infective Endocarditis: A Multicenter, Prospective, Cohort Study. Medicine. 2015; 94(43): 1816.
2. Murdoch D.R., Corey G.R., Hoen B., et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch. Intern. Med. 2009; 169(5): 463-73.
3. Vogkou C., Vlachogiannis N., Palaiodimos L., Kousoulis A. The causative agents in infective endocarditis: a systematic review comprising 33,214 cases. Eur. J. Clin. Microbiol. Infect. Dis. 2016; 35(8): 1227-45.
4. Morpeth S., Murdoch D., Cabell C.H. et al. Non-HACEK Gram-negative bacillus endocarditis. Ann. Intern. Med. 2007; 147: 829–35.
5. Chipigina N.S., Belostotsky A.V. Infective endocarditis: a change in predisposing factors and the evolution of pathogens. Heart: a magazine for practicing doctors. 2010; 9 (4): 242-250 [In Russian].
6. Danilov A.I. et al. Etiology of infective endocarditis in Russia. Clinical microbiology and antimicrobial chemotherapy. 2015; 17 (1): 4-10 [In Russian].
7. Chambers S.T., Murdoch D., Morris A. et al. HACEK infective endocarditis: characteristics and outcomes from a large, multi-national cohort. PLoS One. 2013; 8(5): e63181.
8. Revest M., Egmann G., Cattoir V., Tattevin P. HACEK endocarditis: state-of-the-art. Expert. Rev. Anti. Infect. Ther. 2016; 14(5): 523-30.
9. Durante-Mangoni E., Andini R., Agrusta F., Iossa D., Mattucci I., Bernardo M., Utili R. Infective endocarditis due to multidrug resistant gram-negative bacilli: single centre experience over 5 years. Eur. J. Intern. Med. 2014; 25(7): 657-61.
10. Spencer R.C. The emergence of epidemic, multiple-antibiotic-resistant Stenotrophomonas (Xanthomonas) maltophilia and Burkholderia (Pseudomonas) cepacia. J. Hosp. Infect. 1995; 30 Suppl:453-64
11. Marco Russo, Paolo Nardi, Guglielmo Saitto et al. Paravalvular leak of a mechanical mitral valve prosthesis associated with Burkholderia cepacia subacute endocarditis: a rare case successfully

treated by multidisciplinary approach. Kardiochir. Torakochirurgia. Pol. 2017; 14(3): 200–202.
12. Aggarwal N., Garg S., Pannu H.S., Kler T.S. Fatal Burkholderia cepacia early prosthetic valve endocarditis: a very rare case and a review of the literature. J. Heart. Valve Dis. 2005; 14: 271–274.
13. Valvano M.A., Intracellular survival of Burkholderia cepacia complex in phagocytic cells. Can. J. Microbiol. 2015; 61(9): 607-15.
14. Ho B.T., Dong T.G., Mekelanos J.J. A View to Kill: The Bacterial Type VI Secretion System. Cell Host Microbe. 2014; 15(1): 9–21.
15. Noriega E.R., Rubinstein E., Simberkoff M.S., Rahal J.J. Subacute and acute endocarditis due to Pseudomonas cepacia in heroin addicts. Am. J. Med. 1975; 59(1): 29-36.
16. Shilpa Bhojraj, Zainulabedin Hamdulay, Mohammed Ali et al. Prosthetic valve endocarditis secondary to Burkholderia cepacia. Indian Journal of Thoracic and Cardiovascular Surgery 2007; 23(1): 25–27.
17. Habib G., Lancellotti P., Antunes M.J. 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). E. Heart Journal 2015; 36(44): 3075–3128.
18. Speller D.C.E. Pseudomonas cepacia endocarditis treated with co-trimazole and kanamycin. Brit. Heart J. 1972; 35: 47-48.
19. Pasayan M.K., Cosca K., Domingo G., Saniel M. Infective endocarditis due to Burkholderia cepacia in a patient with a permanent pacemaker. J. Infect. Dis. 2010; 14, Supplement 2: S36
20. Ki H.K., Kim S.H., Han S.W., Cheong H.S. A case of native valve endocarditis caused by Burkholderia cepacia without predisposing factors. BMC Infect. Dis. 2011; 11: 114.
21. Mann T., Ben-David D., Zlotkin A., Shachar D., Keller N., Toren A., Nagler A., Smollan G., Barzilai A., Rahav G. An outbreak of Burkholderia cenocepaciabacteremia in immunocompromised oncology patients. Infection. 2010; 38: 187-194.
22. Martino R., Gomez L., Pericas R., Salazar R., Sola C., Sierra J., Garau J. Bacteraemia caused by non-glucose-fermenting gram-negative bacilli and Aeromonas species in patients with haematological malignancies and solid tumours. Eur. J. Clin. Microbiol. Infect. Dis. 2000; 19: 320-323.
23. Kaitwatcharachai C., Silpapojakul K., Jitsurong S., Kalnauwakul S. An outbreak of Burkholderia cepacia bacteremia in hemodialysis patients: an epidemiologic and molecular study. Am. J. Kidney Dis. 2000; 36: 199-204.
24. Yamunadevi, Ramasubramanian, Senthur Nambi P., Samundeewari, Ramakrishnan N. Outbreak of Burkholderia cepacia bacteraemia in a tertiary care centre due to contaminated ultrasound probe gel. J. Hosp. Infect. 2018 Apr 20. pii: S0195 6701(18)30226-3. doi: 10.1016/j.jhin.2018.04.014. [Epub ahead of print]
25. Speert D.P. Advances in Burkholderia Cepacia Complex. Paediatr Respir Rev. 2002; 3: 230-35.
26. Omar M. El-Halfawy, Marwa M. Naguib, Miguel A. Valvano Novel antibiotic combinations proposed for treatment of Burkholderia cepacia complex infections Antimicrob Resist Infect Control. 2017; 6: 120.
27. Chernukha M.Yu., Alekseeva GV, Sidorenko C.B., Shaginyan IA, Gunzburg A.L. Study of the dynamics of antibiotic resistance of hospital strains Burkholderia cepacia, isolated from patients from Moscow clinics. "The role of clinical microbiology in the prevention of nosocomial infections." Abstracts of the report of the Russian scientific and practical conference with international participation. M. 2004; 93 [In Russian].
28. Centers for Disease Control and Prevention. Burkholderia cepacia in healthcare settings. 2016. https://www.cdc.gov/hai/organisms/bcepacia.html. Accessed 16 Jan 2017.
29. Hamilton J., Burch W., Grimmett G., Orme K. et al. Successful Treatment of Pseudomonas cepacia Endocarditis with Trimethoprim-Sulfamethoxazole. Antimicrob. Agents Chemother. 1973; 4(5): 551–554.
30. Baltimore R.S., Gewitz M., Baddour L.M. et al Infective Endocarditis in Childhood: 2015 Update A Scientific Statement From the American Heart Association Circulation. 2015; 132: 1487-1515.
31. Chipigina N., Vinogradova T., Ozerecki K., Kulichenko V. Thromboembolic complications in Infective Endocarditis. Eur. Heart J. 2006; 27 Abstract Supplement: 3456.

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