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МУЛЬТИДИСЦИПЛИНАРНЫЙ ПОДХОД К ВЕДЕНИЮ ПАЦИЕНТКИ С ПРАВОСТОРОННИМ ИНФЕКЦИОННЫМ ЭНДОКАРДИТОМ НА ПРОГРАММНОМ ГЕМОДИАЛИЗЕ

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Multidisciplinary Approach to the Management of a Patient with Right-Sided Infective Endocarditis on Maintenance Hemodialysis

Резюме

Инфекционный эндокардит у пациентов на программном гемодиализе возникает чаще, чем в популяции, проявляется тяжелыми осложнениями и характеризуется высокой смертностью. В ведении таких пациентов необходимо участие нескольких специалистов. В представленном клиническом наблюдении в сопоставлении с данными литературы обсуждены как типичные характеристики инфекционного эндокардита на программном гемодиализе (стафилококковая этиология, ассоциация с устройствами сосудистого доступа, метаболические и гемодинамические факторы риска), так и особенности конкретного случая (характер нефропатии, приведшей к программному гемодиализу, механизм поражения правых отделов сердца, нечастого для инфекционного эндокардита на программном гемодиализе). Междисциплинарное взаимодействие врачей нескольких специальностей способствовало выбору верной тактики и благоприятному исходу заболевания.

Ключевые слова: *инфекционный эндокардит, сердечно-сосудистые заболевания, программный гемодиализ*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Infective endocarditis in patients on maintenance hemodialysis occurs more often than in the population, manifests severe complications and is characterized by high mortality. The management of such patients requires the participation of several specialists. In the presented clinical observation, both typical characteristics of infective endocarditis on maintenance hemodialysis (staphylococcal etiology, association with vascular access devices, metabolic and hemodynamic risk factors) and peculiarities of a particular case (nature of nephropathy that led to maintenance hemodialysis, mechanism of right heart damage, which is uncommon for infective endocarditis on maintenance hemodialysis) are discussed in comparison with literature data. Interdisciplinary interaction of doctors of several specialties contributed to the choice of the right tactics and a favorable outcome of the disease.

Key words: *infective endocarditis, cardiovascular disease, maintenance hemodialysis*

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AVF — arteriovenous fistula, BP — blood pressure, RRT — replacement renal therapy, IE — infective endocarditis, CT — computed tomography, LV — left ventricle, NSAID — non-steroidal anti-inflammatory drugs, PHD — program hemodialysis, GFR — glomerular filtration rate, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, CKD — chronic kidney disease, HR — heart rate, EchoCG — echocardiography

Infective endocarditis (IE) is a disease with a trend to grow in numbers, serious prognosis and high mortality rates [1]. Among various forms of IE, the origin of this disease in patients undergoing replacement renal therapy (RRT) with dialysis, especially with program hemodialysis (PHD), plays a special part [1, 2]. IE in PHD patients is associated with higher incidence and mortality rates vs. general population [3]; in a majority of cases, it is caused by staphylococcus spp. [2-4], the condition is severe due to comorbidities and suppressed immune system of patients, cardiac valve calcification [4, 5]. Modern RRT methods and infection prevention (bacterial management of solutions and equipment, staff training, adhering to the rules of asepsis while handling vascula access devices), as well as early diagnostics made it possible to reduce the incidence of IE in dialysis patients, but did not eradicate the problem [4]. The management of such patients requires a multidisciplinary cooperation of specialists and team work [1-5]. In the case study, right infective endocarditis (IE) developed in a patient undergoing program hemodialysis, while a comprehensive approach by various healthcare specialists facilitated a favourable outcome.

A 53-year-old female was hospitalised to the Cardiology Department on March 3, 2023 complaining of general fatigue, mixed shortness of breath at moderate physical activity and at rest, fever up to 38^{0}C with chills. According to the patient and medical records, in March 2020 she had her tooth extracted, after a long period (approx. 2 weeks) of NSAIDs the patient experienced weakness, nausea, reduction in diuresis to 50 mL/day. She had a history of approx. 2 years of rare headaches with higher blood pressure (BP), maximum to 180/100 mm Hg; the patient did not take any systematic antihypertensives. Also, for 6–8 years, she often had sudden joint pain (both in small and large joints) and lumbar pain and took NSAIDs without prescription. Physical examination revealed moderate skin pallor, tachyrhythmia (heart rate (HR) of up to 100 bpm), BP of 100/70 mm Hg; organs were unremarkable. Examination demonstrated increased creatinine level up to 890 μmol/L, urea up to 51.8 mmol/L, K^+ up to 6.13 mmol/L, and leukocytosis up to 18–48×10^9/L, reduced Hb level to 108 g/L, increased C-reactive protein (CRP) to 184 g/L (normal value: 0–5), procalcitonin up to 100 ng/L (normal value: < 0.1). The size of kidneys on ultrasound was normal, parenchyma: right — 24 mm, left — 20 mm. Acute kidney injury was diagnosed, which was caused by acute drug-induced tubulo-interstitial nephritis; septic nephropathy (intermittent fever with chills persisted) was not ruled out as well; the eye specialist diagnosed left entophthalmia (the side where the tooth was extracted). Taking into account anuria, hyperazotemia, hyperkalemia, on March 30, 2020 urgent hemodialysis (HD) was initiated using a central venous catheter inserted into the right clavicular vein; all in all, 20 procedures were performed. Examination ruled out HIV infection, viral hepatitis, haemorrhagic fever with renal syndrome, COVID19. Blood culture for sterility was negative; transthoracic echocardiography (EchoCG) did not reveal any pathology. Once RRT was initiated, creatinine reduced to 320 μmol/L, urea to 25.8 mmol/L, K^+ – to 4.13 mmol/L, Hb was 118 g/L, uric acid 420 μmol/L; diuresis returned to 2 L. A 10-day antibacterial therapy (Cefoperazone + Sulbactam (1 g + 1 g) twice daily and Linezolid 600 mg/daily) normalised body temperature and improved overall condition. Later, despite the recommendations (BP monitoring, monitoring of azotemia, uric acid, consultation by rheumatologist, etc.), the patients did not seek medical advice, she was not examined for approximately 2 years and sometimes took various NSAIDs for headache, spine and joint pain. On May 2022, the patient had an episode of acute polyarthritis; uric acid level was measured (600 μmol/L), and the rheumatologist diagnosed gouty arthritis, which was treated with oral Prednisolone 10 mg daily for 10 days; the patient was prescribed Allopurinol, which she did not take. When examined by the nephrologist in June 2022, creatinine level was 278 μmol/L, CKD-EPI glomerular filtration rate (GFR) 14 mL/min/1.73 m^2, urea 18.9 mmol/L, K^+ 5.13 mmol/L, ureic acid 585 μmol/L, Hb 120 g/L, diuresis 1000 mL. Kidney ultrasound: the right kidney is 55x30 mm, parenchyma is 7 mm thick; the left kidney is 56x35 mm, parenchyma is 8 mm thick. Parenchyma echogenicity of both kidneys is higher than

normal, it merges with adjacent tissues, and there are signs of renal scarring. Given persistent hyperazotemia and scarring of both kidneys, stage 5 chronic kidney disease was diagnosed, which is a result of mixed genesis nephropathy (gouty, hypertonic, drug-induced from uncontrolled use of NSAIDs). Taking into account good tolerability of azotemia, it was recommended to continue the conservative therapy of CKD in outpatient settings under supervision of the nephrologist: gastrointestinal adsorbents, gastroprotectors, anaemia correction, antihypertensives, and uricosuric therapy. However, the patient sought a nephrologist's assistance only a half a year later, in December 2022, as her condition was relatively satisfactory. At that time, her laboratory values were as follows: creatinine 319 μmol/L, GFR 14 mL/min/1.73 m^2, urea 55 mmol/L, K^+ 5.1 mmol/L, uric acid 490 μmol/L, Hb 120 g/L, diuresis 1000 mL. On December 21, 2022, a permanent dialysis catheter was implanted into the left clavicular vein and PHD RRT was initiated. On December 23, 2022, an arteriovenous fistula (AVF) formed in the left shoulder, which was complicated with post-surgery thrombosis; on February 3, 2023, an AVF formed in the right shoulder, which was also complicated with thrombosis. On February 25, 2023, the permanent catheter in the left clavicular vein fell out, and purulent discharge was observed at the area of its implantation. A week prior to the current hospitalisation, body temperature rose to 38^{0}C with chills and dry cough.

Upon admission, the patient's condition was severe. Glasgow Coma Scale: 15 points. Height: 161 cm. Weight: 63 kg. Body mass index: 24.3 kg/m^2. Skin and mucosa are pale, without oedema. Left infraclavicular region: skin erythema in the area where the permanent catheter was installed, some amount of purulent discharge. Left and right shoulders: post-AVF surgical scars. Muffled, rhythmic heart tones. The base of the ensisternum: muffled tone I, systolic murmur, which worsens at the peak of intake of breath. Tone II peak is above a. pulmonalis. Heart rate and pulse: 110 bpm. BP is 100/70 mm Hg. Respiratory rate: 22 respirations/minute. In the lungs, breathing is weakened at the scapula level and near the right upper lobe, with wet stridor. Diuresis: 1000 mL. Laboratory findings: complete blood count — leukocytosis (25×10^9/L), high platelet count (680×10^9/L), anemia (Hb 77 g/L). Blood biochemistry: creatinine 294 μmol/L, GFR 15 mL/min/1.73 m^2, urea 9.6 mmol/L, K^+ 4.1 mmol/L, uric acid 490 μmol/L. CRP level increased to 184.6 g/L, procalcitonin — to 90 ng/mL. EchoCG results: left ventricle myocardium mass index (LVMMI) 80 g/m^2, LV ejection fraction 68 %, without impaired local contractility. In the right atrium cavity, there is an irregular, loose, hypoechogenic floating mass with d 5.0x1.6 cm, associated with the tricuspid valve, grade 3 tricuspid valve insufficiency (Fig. 1).

The pulmonary artery systolic pressure is 53 mm Hg. According to chest computed tomography: right-sided multisegmental pneumonia localised in the upper lobe with destruction cavities (Fig. 2). Septic wound discharge and two blood cultures show the presence of methicillin-susceptibl Staphylococcus aureus (MSSA). Kidney ultrasound: no changes vs. June 2022. Otherwise, unremarkable. The patient was diagnosed with right-sided acute infective endocarditis of the tricuspid valve caused by staphylococcus spp., catheter-associated thromboendocarditis (infected blood clot) in the right atrium, cuspid valve insufficiency (grade III regurgitation), right-sided multisegmental pneumonia with destruction cavities.

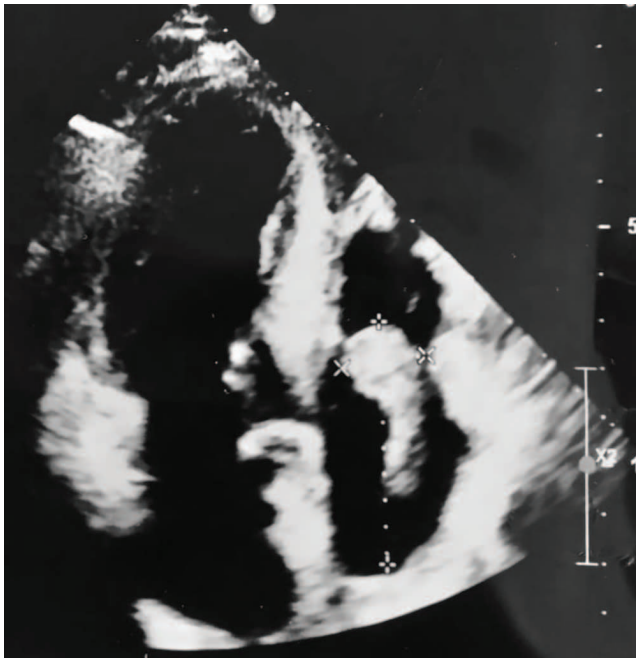

Figure 1. *Echocardiography of the patient. Vegetation on the tricuspid valve, clot in the right atrium (described in the text)*

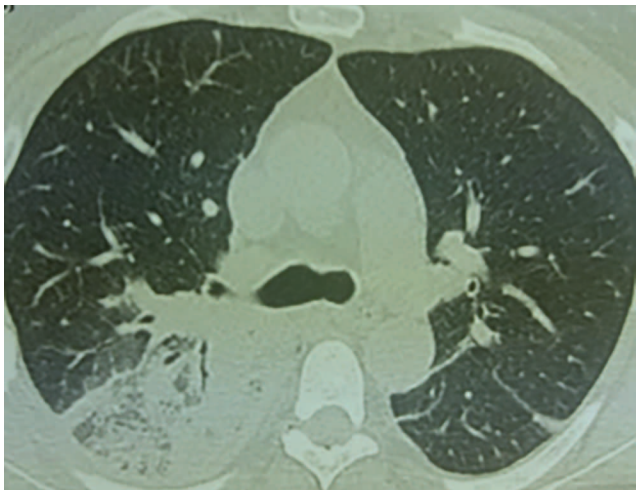

Figure 2. *CT scan of the patient's lungs (description in text)*

The disease developed in a patient with stage 5 CKD from mixed genesis nephropathy (gouty, hypertonic, drug-induced). The diagnosis structure included nephrogenic anaemia, PHD and issues with vascular access (repeated implantations of central venous and permanent dialysis catheters in large veins, recurrent arteriovenous fistulas with blood clotting and catheter-associated blood infection).

Despite the antibacterial therapy prescribed on the basis of an antibiotic susceptibility pattern (Meropenem 3 g daily and Linezolid 600 mg/daily), the patient still had episodes of fever up to 38^{0}C with chills, leukocytosis up to 21×10^9/L, raised CRP levels up to 140.6 g/L, procalcitonin up to 40 ng/mL. Taking into account a permanent source of infection in the heart (vegetation on tricuspid valve cusps, thromboendocarditis), inefficient antibacterial therapy, embolia/septic lung involvement, the IE team coordinated by the heart surgeon decided to undertake a surgery, which was performed on March 27, 2023: vegetation was removed from the entry of the superior vena cava, posterior and septal cusps of the tricuspid valve (De Vega method) using parallel artificial circulation. A histological examination of the removed material confirmed signs of active endocarditis: the sample contained vegetation fragments with fibrin, accumulation of leukocytes, hemagglutinating (for the removed material, please refer to Figures 3, 4, for histological sample — Figure 5). On day three after the surgery, the patient had normal body temperature, leukocyte count reduced to 10.5×10^9/L, CRP to 18.4 mg/L, procalcitonin to 0.44 ng/mL. Creatinine 193.7 μmol/L, urea 4.0 mmol/L, uric acid 410 mmol/L. Blood culture for sterility came back negative. Chest X-ray showed reduction in infiltrative changes.

Given the need in PHD, a permanent dialysis catheter was implanted into the patient's right vena jugularis interna, which is associated with a higher risk of bacteraemia and IE recurrence. Therefore, a decision was taken to keep on trying to form an AVF. The duplex ultrasound scanning of upper limb arteries dd April 5, 2023 revealed haemodynamically significant stenosis of the proximal segment of the radial artery, supplying blood to the efferent vein near the previously formed AVF. On April 11, 2023, the vascular access for extracorporeal dialysis was successfully restored: balloon angioplasty of the stenosis area of the left radial artery and translocation of the AV fistula above the area of the existing blood clot.

Taking into account an increase in the blood flow from 200 mL/min to 660 mL/min, as demonstrated by a follow-up duplex ultrasound scanning of the AVF, starting from April 18, 2023, the AVF is used for PHD. Once the AVF was completely functional, the permanent dialysis catheter in the right vena jugularis interna was removed.

The therapy resulted in steady normalisation of the body temperature without leukocytosis; CRP and procalcitonin level reduced to 11.1 mg/L and 0.1 ng/mL, respectively; Hb was 102 g/L. EchoCG did not show any pulmonary hypertension; condition after plastic reconstruction of the tricuspid valve. Chest CT demonstrated right-sided pneumonia in the upper lobe, recovery phase. Taking into account a high risk of IE recurrence, in the outpatient settings it was recommended to continue antibacterial therapy (Levofloxacin 500 mg daily for 10 days; then antibacterial IE prevention was

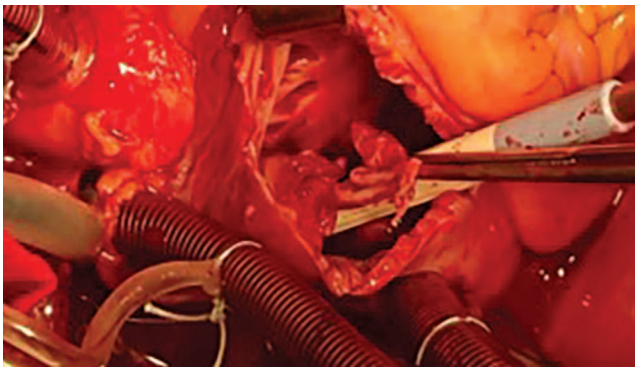

Figure 3. *Large vegetation isolated and removed from the vena cava superior, right atrium, rear and septal flaps of tricuspid valve*

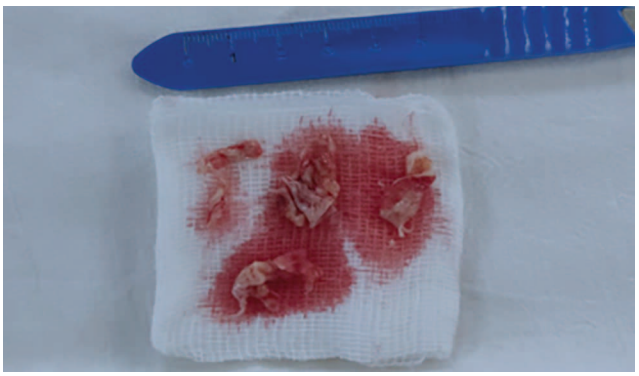

Figure 4. *Remote vegetation*

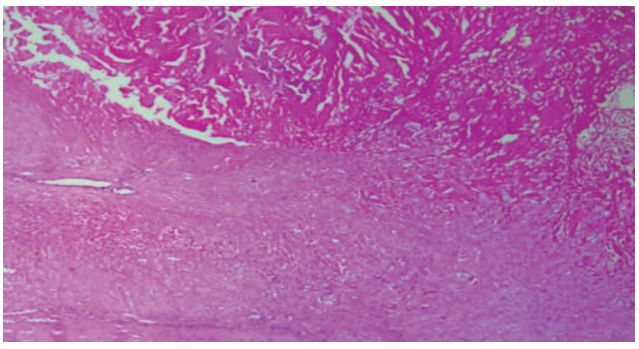

Figure 5. *Vegetation on tricuspid valve (photo): histological signs of fibrin, leukocytes, erythrocytes (hematoxylin/eosin coloration)*

recommended for any invasive dental manipulations), PHD via AVF, follow-up by nephrologist, cardiologist, heart surgeon, vascular surgeon, rheumatologist, monitoring and correction of anaemia, hyperuricemia, systemic inflammation. A 5-month follow-up after surgery by nephrologist, cardiologist and heart surgeon made it possible to record the absence of any signs of recurrent blood infection; the patient's condition was satisfactory. The patient continues PHD and is fully compliant with the drug therapy.

Discussion and Conclusion

1. When analysing the nephropathy in the patient, it is worth mentioning that in this case there were several factors of kidney injury, both acute (a history of sepsis) and chronic (gout, long-term uncontrolled use of NSAIDs, arterial hypertension), and in the absence of drug correction it very soon resulted in kidney scarring, stage 5 CKD and need in dialysis. Among other factors, arterial hypertension was probably the least significant factor (a short period of high BP, no LV hypertrophy on EchoCG), whereas hyperuricemia and NSAID-induced nephropathy were damaging factors for a long time.

2. The patient had two major diagnostic DUKE criteria of IE (two episodes of typical pathogen isolated from the blood flow and vegetation at transthoracic EchoCG) and two minor criteria (febrile fever, septic seeding to lungs and pneumonia), which evidences specific IE [1], the activity of which was completely confirmed by a morphological examination of vegetations removed during heart surgery. An episode of a severe bacterial blood infection (possible odontogenic sepsis) preceded the RRT (lasted for 1.5 years before PHD, IE was ruled out, and the pathogen was not identified), while the reason for the current hospitalisation is staphylococcal IE, preceded by a catheter-associated blood infection. Staphylococcus aureus (usually MSSA) is a leading cause of bacteriaemia associated with vascular access in patients on long-term haemodialysis (up to 75 % of cases) [2] and a prevailing causative agent of IE in this category of patients [3] due to nasal carriage and transfer from the skin during the use of vascular access devices [4].

3. Right-sided IE is observed in patients undergoing haemodialysis considerably more rarely than left-sided IE (0 % to 26 % vs. 75–100 %), both according to literature sources [2, 4, 5], and from our own experience (over 20 years of observation in our inpatient clinic, out of 18 patients with IE undergoing dialysis only 3 patients had right-sided IE). Predominantly left-sided IE is due to a high pressure in the left compartments of heart, which, together with valve calcification caused by phosphor and calcium disturbances in patients with terminal CKD, contribute to mitral and aortic valve damages; the factors of haemodynamic risk of IE are pulmonary hypertension and circulatory overload [5–7]. In the pathogenesis of right-sided IE (a low-pressure system), there is an inflow of infected blood from vascular access devices [5], endothelial damage to large veins, atrial endocardium and tricuspid valve during the implantation and use of a central catheter in the right subclavian vein, as well as microdamage to the endocardium and valve from air bubbles forming as a result of the whirling (turbulent) blood movement in the main system and dialysis unit [5, 7]. The patient had fewer risk factors of left-sided IE: no signs of calcification of valves and vessels on EchoCG due to a short period of the terminal CKD and RRT, no circulatory overload. Literature sources describe a series of observations of right-sided IE with involvement of the superior vena cava and right atrium as direct damage to the endocardium and endothelium by a port-a-cath tip [8]; these examples are very similar to the case study described here. Lung involvement in the patient is typical of right-sided IE (embolic/septic infarctions with destruction) [1].

4. Hyperuricemia as a sign of not only terminal renal failure, but also of gout, is described in the literature as an immune suppression factor contributing to the risk of bacterial infections [9].

5. Antibacterial therapy in patients with IE and PHD should take into account not only the recommended duration (4–6 weeks), pathogen, its microbiological features/antibiotic susceptibility and clinical efficiency [1], but also marked reduction in glomerular filtration rate, as well as the need in correction of antibacterial doses on the basis of clearance characteristics, pharmacodynamics during haemodialysis/hemodiafiltration in patients with stage 5 CKD [7]. In this particular case, attempted consideration of all these factors did not result in the complete efficacy of the antibacterial therapy and was a solid argument in favour of surgery.

6. Indications for heart surgery in patients with IE and PHD are the same as in IE not associated with dialysis [1, 10]. Usually, such patients have a higher risk of unfavourable outcomes of heart surgery due to severe condition [2, 3, 10]. Nevertheless, refusal from or delays in surgery as indicated worsen IE outcomes in patients on PHD [4, 10]. In the real world, timely heart surgery is possible only in large multidisciplinary inpatient clinics having both a heart surgery department and dialysis. The need for such therapy in this case was beyond doubt.

7. An issue of vascular access in IE in patients undergoing PHD requires an individual approach in each case: there are not enough controlled studies of this topic [3]. Possible alternatives are: removal of the catheter and implementation of a new one, temporary transfer of the patient to peritoneal dialysis due to a risk of persistent catheter-associated bacteriaemia [2]. When attempting

to preserve a catheter (e.g., in patients without an alternative vascular access), a longer antibacterial therapy and repeated EchoCG are recommended [4, 5]. The risk of IE in PHD rises when using a central and permanent catheter, and is lower with AVF as a vascular access method [2-4].

Therefore, this case study demonstrates both a common pattern of IE in patients undergoing PHD (association with vascular access devices, staphylococcal aetiology, comorbidity, the need for a multidisciplinary team of specialists) and the characteristics of a certain case (fast nephropathy progression to stage 5 CKD, involvement of the right heart compartments: endothelium of the superior vena cava, endocardium of the right atrium and tricuspid valve). In addition to traditional specialists (cardiologist, clinical pharmacologist, specialist in functional diagnostics), the IE team required participation of nephrologists, RRT specialists, vascular surgeons. Heart surgery was performed as indicated (uncontrolled infection, a large infected blood clot and vegetation in the right heart compartments with septic emboli in lungs), and, together with the antibacterial therapy, it was successful. Practitioners still face the issue of early IE diagnosis in PHD (mostly the use of transthoracic EchoCG), wise aseptic use of vascular access devices, early AVF formation if PHD is required in order to minimise the risk of bacteriaemia, antibacterial IE prevention in case of invasive dental manipulations.

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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