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ЭТИОЛОГИЧЕСКАЯ СТРУКТУРА ИНФЕКЦИОННОГО ЭНДОКАРДИТА У ОТДЕЛЬНЫХ КАТЕГОРИЙ ПАЦИЕНТОВ (ОБЗОР ЛИТЕРАТУРЫ)

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Etiological Structure of Infective Endocarditis in Certain Categories of Patients (Literature Review)

Резюме

В обзоре представлена информация о наиболее частых возбудителях инфекционного эндокардита (ИЭ) среди отдельных категорий пациентов. Основываясь на анализе современных отечественных и зарубежных источников, посвященных изучению ИЭ, в статье описываются условия, предрасполагающие к доминированию тех или иных микроорганизмов у потребителей инъекционных наркотиков, ВИЧ-инфицированных пациентов, пациентов на гемодиализе, с клапанными протезами, пациентов с сахарным диабетом, злокачественными новообразованиями, пожилых пациентов и у беременных.

Рассматривается распределение как типичных для ИЭ (стафилококки, стрептококки, энтерококки), так и редких микроорганизмов, а также полимикробного эндокардита в перечисленных группах. Обсуждаются возможные причины преобладания метициллин-чувствительных или метициллин-резистентных штаммов *Staphylococcus aureus* у разных категорий пациентов с ИЭ, развития заболевания, инициированного редкими для него формами микробных агентов у пациентов с ослабленным иммунитетом, особенности микробной флоры в зависимости от сроков развития клапанной инфекции после протезирования. Несмотря на представления о преобладании того или иного микроорганизма как возбудителя ИЭ в конкретной клинической ситуации, при оказании помощи таким пациентам следует стремиться к точной верификации этиологического фактора для выбора эффективной антибактериальной терапии.

Ключевые слова: *инфекционный эндокардит, этиология, внутривенные наркоманы, ВИЧ-инфицированные, пожилые, беременность, сахарный диабет, злокачественные опухоли, гемодиализ, инфекция протезированных клапанов*

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Abstract

The review contains information about the most common pathogens of infective endocarditis (IE) in certain categories of patients. Basing on analysis of current national and foreign sources concerning IE study there are description of conditions favoring to dominance of various microorganisms in intravenous drug users, HIV-infected patients, patients on hemodialysis, with valve prostheses, diabetes mellitus and malignant neoplasm patients, elderly patients, and pregnant women.

Distribution of both as typical for IE (*staphylococci, streptococci, enterococci*) and rare microorganisms as well polymicrobial endocarditis in mentioned above groups is considered. There is discussion about possible reasons of prevalence of methicillin-sensitive or methicillin-resistant *Staphylococcus aureus* species in different IE patient categories, disease development initiated by rare forms of microbial agents in immunosuppressive patients, microbial flora features depending on terms valvular infection after valve prosthetics. Despite on consideration about predominance of one or another microorganism as an etiologic agent of IE in given clinical situation, during medical help providing it should strive for precise verification of an etiologic factor for choice of effective antibacterial treatment.

Key words: *infective endocarditis, etiology, intravenous drug users, HIV-infected, elderly, pregnancy, diabetes mellitus, malignant tumors, hemodialysis, prosthetic valve infection*

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ART — antiretroviral therapy, DM — diabetes mellitus, HIV — human immunodeficiency virus, HD — hemodialysis, IDU — injecting drug user, IE — infective endocarditis, PVIE — prosthetic valve infective endocarditis

Introduction

Infective endocarditis (IE) is a relatively rare (incidence in general population ranges from 1.5 to 11.6 cases per 100,000) and, at the same time, rather severe disease with a persistently high level of hospitalization (6.9–20.0 %) and annual mortality rate (up to 40 %) [1]. The main causes of poor outcome include severe valvular dysfunction, thromboembolic complications, sepsis, and multiple organ failure. IE course in each case depends on several factors: specific features of the causative agent of the disease, underlying diseases and comorbidities, the presence of immunodeficiency, and potential genetic predisposition in certain patients [1, 2]. Obviously, the properties of the causative agent (various pathogenic power and virulence factors, massive infection and route of entering the bloodstream, resistance to antibiotics) largely determine the clinical scenario of IE, and the fight against an infectious agent, i.e., reasonable antibacterial therapy remains the main line of the management of this disease in the 21st century. Detection of etiology based on the results of bacteriological, less often — of serological blood tests is a major diagnostic criterion for IE indicated in international consensus documents [3, 4]. However, in real-life clinical practice, one often has to start empirical antibiotic treatment for IE (prior to getting the results of blood culture, or if they are negative) [5, 6] assuming the most likely pathogen in a particular case. In such cases, the most correct assumption of a probable etiological factor based on the assessment of medical history and clinical setting can significantly help in choosing the optimal empirical antibiotic therapy regimen, therefore, it can have a positive effect on the disease outcome [7].

The etiology of IE has undergone certain changes since the first bacteriological study performed at the end of the 19th century [8]. Thus, streptococci, being the “leaders” of the infectious process in IE at the end of the 19th — early 20th century, gave way to

staphylococci [9]. However, IE still remains predominantly a gram-positive infection with the leading etiological role of staphylococci, streptococci, and enterococci [2]. The changes in the etiological structure of IE are associated with the increased number of invasive diagnostic and therapeutic procedures: cardiac surgeries, implantation of pacemakers, hemodialysis, as well as intravenous administration of drug products and narcotic drugs [2].

Patients with diabetes mellitus (DM), individuals infected with the human immunodeficiency virus (HIV), and patients taking drug products that suppress their immune system (for example, for autoimmune, malignant diseases, organ transplantation, etc.) are at the highest overall (non-cardiac) risk of IE. This review provides up-to-date information on the most likely causative agents of the disease in certain groups of patients, in particular, in injection drug users, HIV-infected patients, patients on hemodialysis, patients with DM, malignant neoplasms, as well as in pregnant women and the elderly.

The Role of Microbiology Testing in the Diagnosis of Infective Endocarditis

Since 2000, the diagnosis of IE is based on the Modified Duke Clinical Diagnostic Criteria (developed at Duke University, Durham, USA) that were extended with the detection of *S. aureus* in blood culture, regardless of the route of infection, as well as with bacteriological and/or serological evidence of *Coxiella burnetii*, and results of transesophageal echocardiography (Table 1) [3].

A positive result of blood culture is one of the two major diagnostic criteria for IE, therefore, the identification of the causative agent is the most important step in diagnosis and a reliable parameter for choosing an adequate antibacterial drug. Blood culture allows identifying the pathogen and checking its sensitivity to antibiotics.

The absence of culture growth during routine microbiological test suggests that the etiological factor includes pathogens that are rarely associated with endocarditis.

Table 1. *Modified Duke criteria with 2015 ESC additions [4].*

Major criteria
Blood culture positive for IE
a. Typical microorganisms consistent with IE from 2 separate blood cultures: • *Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus* **or** • community-acquired enterococci, in the absence of a primary focus **or**
b. Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: • at least 2 positive cultures of blood samples drawn 12 h apart **or** • all of 3 or a majority of >4 separate cultures of blood (with first and last sample drawn at least 1 h apart) **or**
c. Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer 11 : 800
Imaging methods are positive for IE
a. Echocardiogram positive for IE • vegetation • abscess, pseudoaneurysm, intracardiac fistula • perforation or valve aneurysm • new partial dehiscence of prosthetic valve.
b. *Abnormal activity around the site of prosthetic valve implantation detected by 18F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT.*
c. *Definite paravalvular lesions by cardiac CT.*
Minor criteria
1. Predisposition such as predisposing heart condition, or injection drug use.
2. Fever as temperature >38°C.
3. Vascular phenomena *(including those detected by imaging only)*: major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

The diagnosis of IE is considered definitive if:	**The diagnosis of IE is considered possible in the presence of:**
2 major criteria **or**	1 major criterion and 1 minor criterion **or**
1 major criterion and 3 minor criteria **or**	3 minor criteria
5 minor criteria	

Note: additions of the European Society of Cardiology are in italics [4]
^{18}F-FDG — fluorodeoxyglucose; HACEK — *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*; IE — infective endocarditis; CT — computed tomography; SPECT — single photon emission computerized tomography; PET — positron emission tomography

These may be, for example, non-toxigenic, extracellular bacteria that require complex feed conditions for their growth in laboratory, as well as fungal flora or intracellular pathogens (in particular, *Coxiella burnetii, Chlamydia, Tropheryma whipplei*) that cannot be identified in routine clinical practice [10].

To identify these microorganisms, an extended bacteriological test is recommended, including blood culture on chocolate agar, as well as serological, immunological, and immunohistochemical methods. The results of polymerase chain reaction in blood tests and of the resected surgical material of valve tissue or embolic fragments are extremely important [11].

Etiology and Special Aspects of the Pathogenesis of Infective Endocarditis in General Population

Among the causative agents of IE, coccal flora is prevailing: staphylococci and streptococci cause 70–80 % of cases [12]. *S. aureus* remains the predominant pathogen that causes IE in 25–30 % of cases, while the proportion of coagulase-negative staphylococci is 8–11 % [12]. Streptococci, mainly of *Viridans* group, cause the disease in about 30 % of cases. Gram-negative microorganisms, including those of HACEK group (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella* subspecies), are the causative agents of IE in 3–5 % of cases; much less often this disease is caused by non-HACEK pathogens, such as *Escherichia coli, Pseudomonas aeruginosa*, *Klebsiella* strains, *Serratia, Proteus mirabilis, Stenotrophomonas maltophilia, Enterobacter cloacae*, etc. [10].

Fungal flora rarely (up to 2 %) serves an etiological factor for IE and is found mainly in immunosuppressed patients [5].

According to the present-day concept, microbial vegetation development starts with the entry of bacteria into systemic flow via oral cavity, gastrointestinal or urogenital tract, or skin (microtrauma, pustular infections), venous catheters, or after invasive diagnostic or surgical procedures. Bacteremia, being the first stage in pathogenesis events, initiates the subsequent ones, namely, adhesion and colonization [13]. During the second stage, i.e., adhesion, bacteria (especially gram-positive ones) attach to abnormal or damaged endothelium with the help of surface adhesins [13]. These specific proteins act as mediator of bacterial adhesion to host extracellular matrix proteins; this process is facilitated by platelet microthrombi and fibrin. Finally, bacterial adhesion promotes the growth of the colonies of microorganisms when bacterial reproduction takes place simultaneously with the migration of white blood cells, infiltration, and inflammation that result in the development of a mature vegetation [14]. Biofilm that can be produced by most of the microorganisms that cause IE protects them against the host immune response. This protective mechanism allows a bacterial cluster entering the extracellular mucus-like matrix with quorum sensing and synchronization of gene expression that accelerates the development and maturation of vegetation [14].

Infective Endocarditis in Intravenous Drug Users

The problem of the illegal use of drugs remains relevant in today's context. According to the international report [15], in 2019, a total of 275 million people used illegal drugs; this value is 22 % higher compared to the year 2010. The number of injection drug users is over 11.0 million (range 8.9 to 14.2 million) [15]. The most severe bacterial complications in injection drug users (IDUs) are endovascular infections, including IE, with the incidence in this category of patients 8.0–37.8 % of the total number of cases [16].

Conditions for bacteremia development in IDUs include: infections of skin and soft tissues; using saliva as a solvent for a narcotic substance; injections in non-sterile conditions, and the repeated use of devices for the preparation of injected drugs [17]. IDUs are the risk group for developing IE due to frequent comorbidities that have an immunosuppressive effect (HIV infection, hepatitis C). The abovementioned characteristics of such patients results in the high incidence of IE that is almost 20-fold compared to the general population (1.5 to 3.3 cases per 1,000 IDUs per year) [16].

IE in IDUs differs from that in general patient population. The disease is more common in young patients [18]; damage to the right heart is known to be predominant (up to 76–90 % of cases) with the development of severe complications: sepsis, heart failure (HF), and embolism [19]. In addition, there are cases of IE in injecting drug users with and atypical course — without fever [20].

Like in general population, *S. aureus* is the microorganism that most often causes IE in IDUs (up to 77.2 % of cases of IE in drug users vs 39.6 % in the patients in general population) [8, 21, 22]. It is associated with higher skin colonization by *S. aureus* (probably due to the frequent damage of its integrity) in IDUs compared to the individuals who use drugs only orally. Damage of skin with a needle provides a direct entry of microorganisms into the bloodstream. Papers with the analysis of the disease in IDUs published in recent years describe the prevalence of the methicillin-sensitive strain of *S. aureus* over the methicillin-resistant one [18, 21–23]. W. Lorson et al. (2019) emphasize the etiological significance of the methicillin-resistant strains of *S. aureus* and

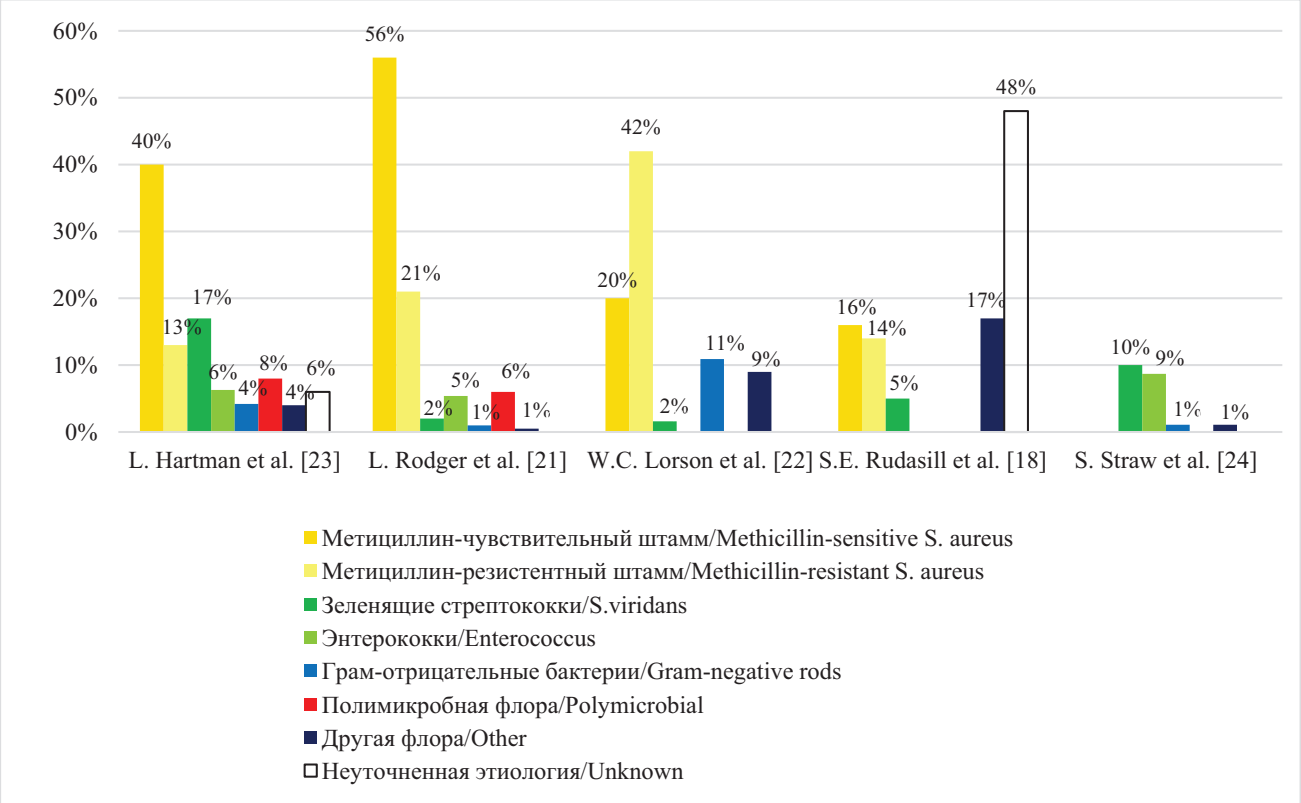

Figure 1. *The etiological structure of infective endocarditis in injection drug users*

Pseudomonas in the development of IE in IDUs, as well as the need to use antibiotics that are active against these pathogens [22].

Streptococci can also be an etiological factor for IE in IDUs. Detection rate of the bacteria of streptococcus group (*Viridans* group, enterococci, other streptococci) in the analyzed works ranged from 2 to 20 % (Figure 1) [18, 21–24].

Streptococcus pyogenes or group A *streptococcus* were previously considered to be relatively rare causative agents of IE both in general population and in IDUs. However, M. Rebechi et al. in their report (2021) mentioned the increased number of IE cases caused by *S. pyogenes* or group A *S.*; 16 (89 %) out of 18 patients with IE of the indicated etiology took injection drugs [25].

In addition to staphylococci and streptococci, IE in IDUs can be caused by rare causative agents with a higher incidence of pseudomonas, fungal strains, and polymicrobial combinations [26].

Polymicrobial endocarditis is rare, however, it is characterized by high mortality, especially in cases when the combination of microorganisms includes the representatives of *Candida* family [26]. The most common is the combination of *S. aureus* and *S. pneumoniae*; the second most frequently described combination is *S. aureus* and *Pseudomonas aeruginosa* [22]. Polymicrobial endocarditis has been described particularly in IDUs; it is often accompanied with the damage to several heart valves [26]. Management of such patients is associated with significant difficulties, primarily due to resistance to common combinations of antibacterial drugs. Chances of a favorable disease outcome can be increased only with a combination of long-term intravenous administration of antibiotics in combination with antifungal drugs, and, if necessary, with timely surgical treatment [26].

Using saliva as a solvent for intravenous drug injections may cause the growth of conventionally nonpathogenic organisms in IDUs with IE, such as *Haemophilus parainfluenzae, Eikenella corrodens* and *Streptococcus miller* [16, 17].

Obviously, if the right heart is affected and there is evidence or suspicion of intravenous drug use, or if a venous catheter is placed, then the initial choice of empiric antimicrobial therapy is aimed to manage *S. aureus.*

Etiology of Infective Endocarditis with Underlying HIV Infection

Analysis of the etiological aspect of IE in this category of patients requires considering both the aspect of intravenous drug use and the state of immune system, including the presence/absence of antiretroviral therapy

(ART). IE in patients with HIV infection is uncommon [4], predominantly in IDUs [27]. Therefore, staphylococci are the prevailing etiological factor in this group of patients [4]. A certain etiological role in IE development in the setting of immunosuppression belongs to pathogenic yeast fungi (especially with the intravenous administration of heroin dissolved in lemon juice) and gram-negative flora [4, 22]. In HIV patients at the AIDS stage, especially in the absence of ART, there is increased etiological significance of other microorganisms that are not actual causative agents of IE in patients without immunosuppression. For example, there are case reports of Salmonella IE at the late stages of HIV/AIDS in the absence of ART in patients with diarrhea caused by simultaneous intestinal damage by cytomegaloviruses [28]. Enterococcal IE in non-IDU patients with advanced HIV infection was also attributed to severe bowel disease [28]. The probability of enterococcal IE is increased in HIV patients who receive frequent repeated courses of antibiotics to prevent and manage various infections that inhibit the growth of other microorganisms [8, 28]. Less common or rare etiological factors include *Pseudomonas spp.*, *Xanthomonas maltophilia*, *Neisseria spp.*, *Corynebacterium spp.*, coagulase-negative staphylococci, mature *Erysipelothrix*, *Gemella morbillorum, Citrobacter spp., Haemophilus spp.,* and *Eikenella corrodens* [22]. Finally, about 5 % of IE cases are caused by a polymicrobial infection [28].

Infective Endocarditis in Hemodialysis Patients

All patients on renal replacement therapy are at risk of infections, including IE. Predisposing conditions include the specific aspects of a particular method: hemodialysis (HD) requires repeated access to the vascular system through an intravenous catheter or a permanent arteriovenous fistula that leads to frequent episodes of bacteremia; peritoneal dialysis requires a dialysis catheter placed in abdominal cavity; kidney transplantation involves lifelong immunosuppressive therapy. Another risk factor for IE development of heart valve calcification in patients with end-stage renal disease [29] that is caused by the disorder of calcium and phosphorus metabolism with underlying secondary hyperparathyroidism and chronic inflammation.

The source of bacteremia that is often observed in patients on long-term HD (in more than 70 % of cases with a central line catheter) [30] can be both endogenous (opportunistic skin flora) and exogenous foci of infection (hands of medical personnel, equipment).

Opportunistic skin pathogens and *S. aureus* are the main causes of vascular access-associated bacteremia in patients who receive long-term HD (up to 75 % of cases) [30, 31]. Other bacteria that cause IE in patients on renal replacement therapy include coagulase-negative staphylococci, *Streptococcus* group, *Enterococcus* group, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa* [30, 31].

Over the recent years, the increased incidence of methicillin-resistant *S. aureus* strains is observed in HD patients; according to different authors this value amounts up to 40 % of IE cases [31]. *Candida* species are found extremely rarely. At the same time, the results of blood culture tests are quite often negative; this fact is most often associated with the previous use of antibacterial agents that significantly complicates the following treatment [32].

H. Jeon et al. in their paper (2020) analyzed the relationship between the type of vascular access (temporary/catheter or permanent access) and the route of infection in patients who underwent the HD procedure and were hospitalized with a diagnosis of IE (96 individuals) [33]. Fifty-seven of them had a permanent dialysis catheter. A hemodialysis access site was in most cases (82 %) identified as the main source of infection. The most common causative agent of endocarditis in both the catheter access group and the permanent access group was methicillin-susceptible *S. aureus* that was the cause of the disease in more than a third of cases. More cases of enterococcal endocarditis were observed in the catheter access group than in the permanent access group (27 % vs 8 %, p = 0.03). A total of 4 cases of IE caused by vancomycin-resistant enterococci were reported.

Native Valve Infective Endocarditis in Patients with Diabetes Mellitus

Studying the specific features of IE in patients with DM is required primarily due to the significant number of such patients and the increasing prevalence of DM throughout the world. According to the World Health Organization, 422 million people had diabetes in 2014; moreover, this value has tripled since 1980 [34]. Observed population aging and generally increasing incidence of obesity will obviously contribute to the currently growing DM morbidity rate. Immune dysfunction in patients with DM contributes to the development of infectious complications, including sepsis and IE. In addition, patients with DM are prone to severe endothelial dysfunction that is one of the main pathogenetic stages in the development of IE. DM has been actually identified as a risk factor for poor prognosis in various bacterial infections, including IE [35].

The high prevalence of DM in patients with IE is confirmed by recent large-scale studies performed by

T. Abe et al. (USA) [36] and J. De Miguel-Yanes et al. (Spain) [37]. During analyzing the specific features of IE with underlying DM, the authors of these two researches also compared the etiological structure of the disease in groups of patients with and without concomitant DM.

Patients in the DM group in the Spanish analysis predominantly had such microorganisms as *S. aureus* (14.7 % vs 13.2 %; p = 0.07) and enterococci (16.2 % vs 14.2 %; p = 0.02), while *Viridans streptococci* (18.9 % vs 21.8 %; p = 0.003) were found more often in the patients without concomitant DM [37].

A similar distribution of IE causative agents was found in the analysis carried out by American researchers. Patients with DM more often had *S. aureus* (35.6 % vs 33.1 %; p < 0.001), other staphylococci (6.7 % vs 5.4 %; p < 0.001), enterococci (7.6 % vs 6.5 %; p < 0.001), group B streptococci (1.6 % vs 1.3 %; p < 0.001), and gram-negative organisms (4.8 % vs 3.8 %; p < 0.001) [36].

The authors conclude that the reason for the higher detection rates of staphylococci, enterococci and gram-negative microorganisms may include more frequent hospitalizations of patients with DM for various reasons that contribute to the development of hospital-acquired infections. The high probability of infection with *Staphylococcus aureus* is one of the reasons for poor clinical outcomes in patients with DM and IE, due to the tendency to abscess development and valve destruction that require aggressive antibiotic therapy and early surgical treatment [36].

Infectious Endocarditis in Pregnant Women

Knowledge about IE during pregnancy is limited by the extremely low prevalence of the disease in this group (≈1 case of IE per 100,000 pregnant women) [38]. As a rule, the disease develops secondary to a pre-existing lesion of the cardiac valvular apparatus that may be congenital, less often — rheumatic, or due to intracardiac foreign bodies, or intravenous drug use. As in the general population of non-pregnant patients with IE, there is increased number of reported cases of IE in pregnant women associated with intravenous drug use [38, 39].

Despite the low incidence of IE during pregnancy, maternal mortality amounts to 33 %; in addition, pregnant women with IE have a high incidence of embolic complications and mycotic aneurysms [39]. An erroneous interpretation of several nonspecific symptoms of intracardiac infection (tachycardia, shortness of breath) as hemodynamic changes that are common during pregnancy often makes it difficult to diagnose IE and to start antibiotic therapy timely [40].

In a systematic review of the cases of IE in pregnant and postpartum women, K. Kebed et al. (2014) analyzed maternal risk factors, microbiological profile, as well as both maternal and fetal outcomes [39].

Ninety cases of IE were identified in pregnant and postpartum women. The most frequently detected causative agents were streptococci and staphylococci in 39 (43.3 %) and 23 (25.6 %) women, respectively. Results of culture tests were negative in 8 women (8.9 %), and polymicrobial IE was found in 3 (3.3 %) women.

Localization of IE in the left heart (43 cases with localization on one valve and 6 cases with damage to two valves) was more often observed with streptococcal causative agents compared to staphylococcal ones.

According to the results of the analysis of literature sources for 15 years (1997–2013), S. Yuan has analyzed 30 cases of IE in pregnant women at different periods of pregnancy [41]. Among them, one or two pathogens were found in blood culture or vegetation culture tests in 21 patients. According to the conclusions made by the author, the predominant infectious agent in pregnant women with IE was *Staphylococcus aureus* (38.1 %), the second most common was *Streptococcus viridans* (19 %). The following microorganisms were obtained in culture tests with the same frequency (9.5 %): *S. mitis, S. aureus* with *H. parainfluenzae*, group A α-hemolytic streptococci, *S. agalactiae, S. mutans* with *S. sobrinus, S. sanguis, Salmonella typhi*, and *H. parainfluenzae*. In general, in the study performed by S. Yuan, different species of streptococci caused 48 % of IE cases. *Staphylococcus aureus*, alone or in combination, was isolated in 9 (43 %) cases of IE.

IE of tricuspid valve during pregnancy and after abortion is more often caused by group B streptococci. These bacteria can be isolated from the genital area in 5–40 % of women and also cause the development of neonatal sepsis, chorioamnionitis, endometritis, and maternal bacteremia. Endocarditis in pregnancy is sometimes caused by rare microorganisms. In particular, there are case reports of IE with the following infective agents: *Bacillus cereus, Abiotrophia defectiva, Staphylococcus lugdunensis, Candida parapsilosis*, etc. [41].

Infectious Endocarditis in Elderly Patients

Over the past 50 years, there has been a definite trend towards the increasing incidence of IE in elderly patients [42]. The incidence of IE in people 70+ in different countries is 14.5–20.0 cases per 100 thousand people per year [2, 42].

Specific features of IE etiology in the elderly are due to several characteristics that are typical to this age group. Year by year, we observe the increasing number of elderly patients with prosthetic valves, with hospital-acquired infection due to frequent hospitalizations

and invasive examination methods [2]. About half of all cases of hospital-acquired IE in elderly patients are associated with intravascular catheters and other invasive devices.

Malignant neoplasms, DM, and pathologies of urogenital and digestive tracts are more common in elderly patients [43].

Summarizing the results of studies evaluating the characteristics of IE causative agents in elderly patients (> 65–70 years) compared with younger patients, one should mention the increased frequency of detection of enterococci, *S. bovis*, as well as the relatively decreased number of endocarditis cases caused by *S. viridans*, as well as by *S. aureus* (Figure 2) [42].

Methicillin-resistant and coagulase-negative strains prevail among the staphylococci that are most commonly associated with nosocomial IE [51, 52].

Increased incidence of IE in elderly patients that is caused by enterococci is associated with a higher incidence of inflammatory and oncological diseases of the colon, as well as with frequently performed instrumental procedures for urological and gastrointestinal tracts. IE caused by *S. bovis* is also most commonly associated with neoplastic diseases of large intestine [53].

Elderly patients typically develop IE as a result of the overlay of a hospital-acquired infection that is mainly represented by *S. aureus*. Percutaneous procedures most often cause the development of staphylococcal IE, and procedures on urinary tract — the enterococcal one [4]. Besides, various types of oral streptococci also belong to the causative agents of endocarditis.

As a rule, a prosthetic valve IE demonstrates coagulase-negative oxacillin-resistant staphylococcus in the results of a culture test.

Patients with IE who are in nursing homes often have microorganisms that are resistant to antibiotics: methicillin-resistant staphylococci, vancomycin-resistant enterococci, as well as penicillin-resistant pneumococci [52].

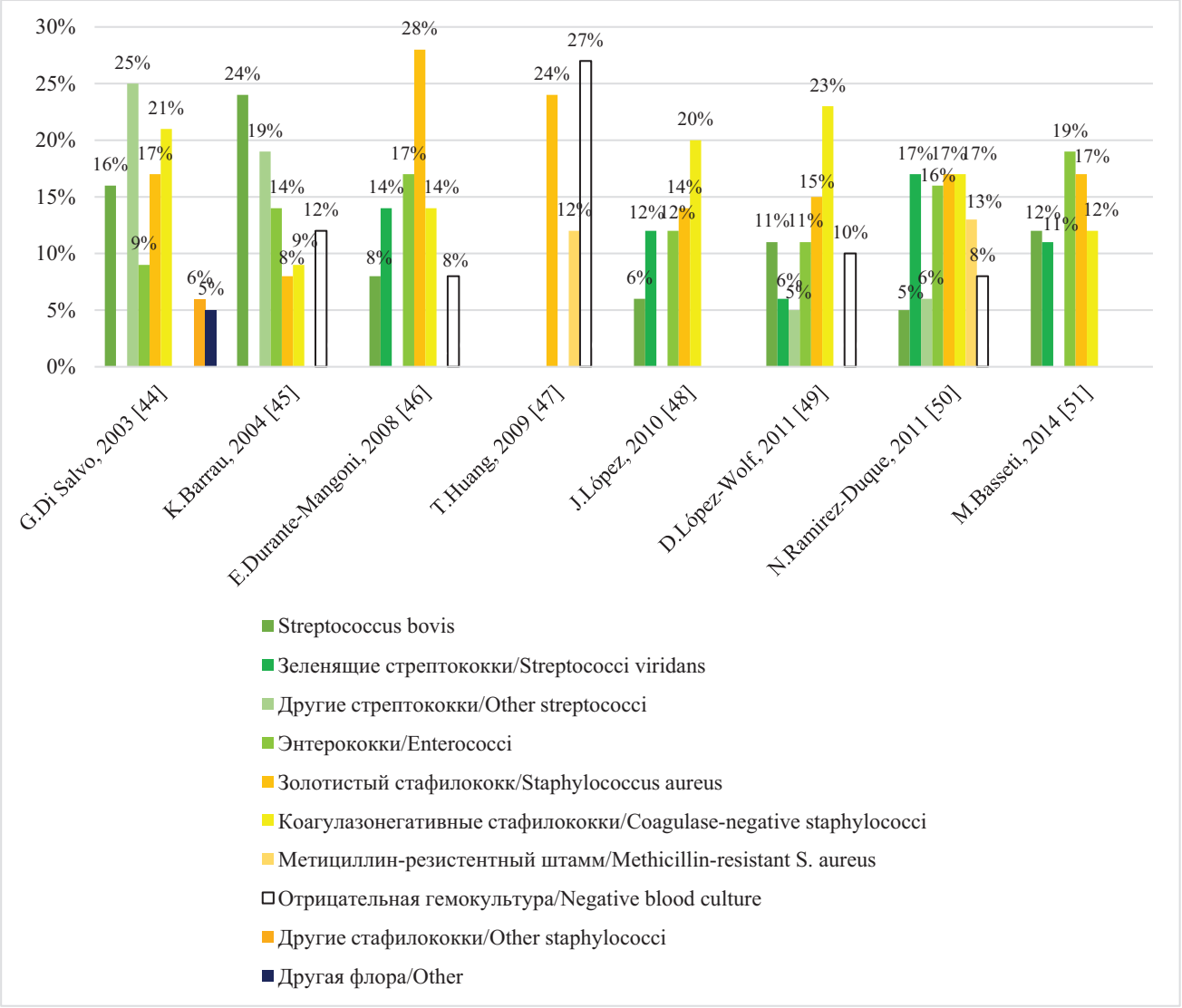

Figure 2. *Characterization of causative agents of infective endocarditis among the elderly*

Gram-negative rods and fungal flora are most commonly found in patients on parenteral nutrition. Causative agents of HACEK group, as well as fungi, are found relatively rare, in 1–5 % of cases [42]. Quite often (8–27 %) one cannot identify the causative agent of the disease [4].

Infective Endocarditis and Malignant Neoplasms

The problem of IE associated with malignant neoplasms is currently of considerable interest due to both increased incidence of IE in elderly patients and increased incidence of malignant tumors in this category of patients [54]. According to the 2015 European Society of Cardiology guidelines, IE in cancer patients is defined as a special type of this disease [6]. Depending on the "mode of entry" of the infection and the clinical situation, the combination of IE with cancer results in bacteremia both with causative agents that are typical for IE (*S. mitis, S. gallolyticus*, other group D streptococci, enterococci, *S. aureus*) and with microorganisms that are rarely found in IE patients (*Lomentospora prolificans*) [54]. Discussed mechanisms that can explain IE development along with neoplasms include bacteremia (a consequence of tumor decay, increased mucosal permeability after frequent invasive medical and diagnostic procedures); immunosuppression induced by chemotherapy and radiation therapy; development of non-bacterial thromboendocarditis caused by hypercoagulation; and age-related changes (marantic endocarditis) [54]. Patients with past IE have the increased probability of malignant tumors, in particular, colorectal cancer and hepatocellular carcinoma that persists for several years [55]. Cases of IE were described in patients with lymphoproliferative diseases, lung, breast and prostate cancer. However, IE develops more often in patients with tumor lesions of colon and rectum than in patients with cancer of other localizations, notably, with a proven etiological importance of *Streptococcus bovis/gallolyticus*. The association of the specified etiological factor of IE in elderly patients with intestinal malignant neoplasms allows considering IE caused by *Streptococcus bovis/gallolyticus* as a marker of a possible oncological pathology with a recommendation for repeated colonoscopy to detect an intestinal tumor both during IE period and in subsequent years [56].

Prosthetic Valve Infective Endocarditis

Prosthetic valve IE (PVIE) develops in 2–10 % of patients during the first year after prosthetics with an incidence of approximately 0.5 % per year in subsequent years; more often — after aortic valve replacement; it equally affects mechanical and biologic prostheses [4]. Early onset of PVIE (especially earlier than 2 months after surgery) is caused by surgical infection with antibiotic resistant bacteria (*S. epidermidis*, diphtheroids, coliform bacilli, *Candida*, *Aspergillus*) or by infection through vascular access devices in the early postoperative period (*S. aureus*) [4]. Late development of PVIE, especially later than 12 months from the day of surgery, is caused mainly by the episodes of transient bacteremia during medical interventions. Microbial flora in late PVIE is almost identical to that in that cases of native valve IE (streptococci, *S. epidermidis,* diphtheroids, gram-negative flora species *Haemophilus*, *Actinobacillus actinomycetemcomitans*, and *Cardiobacterium hominis* [4, 57]. Mortality in patients with prosthetic endocarditis caused by *Staphylococcus aureus* and fungal flora reaches 70 %; survival is significantly higher in patients who underwent surgical removal of affected and infected valves with debridement of the affected areas and prosthesis replacement [58]. PVIE caused by *Pseudomonas aeruginosa* and multidrug-resistant enterococci demonstrates poor response to drug treatment [57]. Generally, the diagnosis of PVIE requires advanced methods of cardiac imaging, and indications for cardiac surgery are determined by the Endocarditis Team [4]. Patients with valve prostheses are at the highest risk of IE development and require antibiotic prophylaxis before invasive medical procedures [4, 14].

Conclusion

Today, in the 21st century, IE remains predominantly a gram-positive infection; staphylococci, streptococci, and enterococci are the "leaders" in a wide range of pathogens that can cause IE. This is evidenced by the analysis of IE etiology both in general patient population and in certain categories of patients. Gram-negative, anaerobic, and fungal flora are defined as the causative agents of IE with a significantly lower frequency. Specific etiological aspects of IE in different groups of patients are determined to a large extent by the massive infection and the route of entering of the causative agent into patient's body. Analysis of a possible source of bacteremia should become an important algorithmic part of the medical records for patients with IE (previous medical procedures and interventions, infectious diseases of skin and soft tissues, nasopharynx, state of teeth and oral cavity, permanent vascular access devices, heart foreign bodies, repeated intravenous injections, etc.). Age, hygiene habits, conditions of development (in or out of the hospital), and the nature of comorbidities can also affect the prevalence of certain causative agents in each case of IE (degree of the contamination of skin and mucous membranes, intestinal colonization), as well

as the immune response of macroorganism (DM, HIV infection in the absence of ART, chemotherapy for malignant neoplasms). However, despite the required clinical assessment of the characteristics of the alleged causative agent for empirical antibiotic therapy, one should aim for an accurate etiological diagnosis of IE by bacteriological and serological methods. A positive result of blood culture test is one of Duke's major diagnostic criteria that allows performing effective antibiotic treatment and predicting the course of the disease.

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