Current Opinions in Infective Endocarditis

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Infective endocarditis (IE)[1-7] constitutes an infection of the cardiac valves or of the endocardium wall from bacteria, fungi and less commonly rickettsia, chlamydia and probably viruses. The term was first used by Thayer in 1930 and is preferred to the older "bacterial endocarditis" since it includes the whole spectrum of microorganisms that affect the endocardium.

Before the antibiotics era, infective endocarditis constituted a progressive, untreatable disease with fatal outcome, that usually affected young individuals. In the last 50 years, however, the wide use of antibiotics on the one hand and the development of heart surgery, on the other hand, brought about two significant changes. The first was the significant reduction of mortality and the conversion of the disease to treatable in the majority of cases, on condition that there would be a timely diagnosis and a quick onset of treatment. The second change involved the change of vulnerable population and the alteration of infectious agents responsible for the pathogenesis of the disease. More analytically, the incidence of rheumatoid valvulopathy has been dramatically reduced, while there has been an increase of the rate of individuals with prosthetic valves and/or permanent pacemaker in conjunction with an ongoing increase of immunosuppressed patients. It is thus easy to explain the increase of the mean age of patients affected by infective endocarditis to a range above 50 years of age. Another change in the epidemiological scenery of endocarditis is the wide use of intravenous drugs and an increase in the number of individuals with mitral valve prolapse. Despite the above, it seems that the incidence of the disease (almost 20 cases / 1,000,000 population / year)[2,4,8] has, to date, remained the same as in the pre-antibiotics era.

Moreover, changes have been made in the last few years in the diagnosis of the disease and new causative factors have been added. The development of new microbiology techniques and the evolution of the older ones revealed the role of many new pathogenic microorganisms, such as *Coxiella burnetii*, Brucella, Bartonella and fungi. Furthermore, the development of heart ultrasound and the contribution of its findings to the establishment of Durack diagnostic criteria (Duke criteria), that replaced the older von Reyn ones (Beth Israel criteria), constituted an important step towards the better diagnosis of the disease.

Epidemiology - classification - pathogenic causes

The disease affects mainly males, with a ratio of 2.5:1, 50 years old and above[6,9-12].

In the past, IE was classified to *acute* (normal valve affected by a highly virulent microorganism, such as staphylococcus aureus, with a rapid destruction of the valve, metastatic infectious foci and rapid death) and *subacute* (patho-

logic valve and low virulence microorganism, such as streptococcus viridans, with a mild, insidious onset and long duration)[2,37].

Today, when such typical IE cases are less common, thanks to the use of antibiotics, the classification is based on the anatomical condition of the heart. IE is divided into native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE)[7].

1. **In NVE**, 60-80% of the individuals (with the exception of intravenous drug addicts) present a pre-existing heart lesion. Mitral valve prolapse is the most common abnormality in adults, ranging from 30% to 50%[2]. It should be noted that although the rate of individuals suffering from mitral prolapse, affected by IE is low, the significance of this valvulopathy however is great because it has high prevalence (2%-6% in the general population)[7,13].

The rate of rheumatoid valvulopathy has decreased today below 30% and it mainly affects middle age and/or the elderly population, since the incidence of rheumatoid fever nowadays has been reduced universally thanks to the use of antibiotics [2,12].

Streptococci viridans still constitute the predominant cause (excluding again intravenous drug addicts)[10,13], responsible for approximately 40% of NVEs. They are part of the oropharyngeal natural flora and they do not constitute a species but a group of microbes (Streptococcus viridans group), that includes among others *Streptococcus sanguis*, *S. mutans*, *S. milleri* and *S. mitis*[14]. They are usually penicillin - sensitive.

25-30% of NVEs is attributed to staphylococci[2,10]. *Staphylococcus aureus* (coagulase +) is 5 times more frequent than *S. epidermidis*. It often affects healthy valves and due to its high virulence, the symptoms are intense with often metastatic abscesses, rapid destruction of the affected valve, leading to patient's death in just a few weeks. In contrast, *S. epidermidis* (included together with other species, such as *S. lungdunensis*, in the category of coagulase (–) staphylococci) affects pathological valves and has a long course. The vast majority of staphylococci are penicillin resistant and the rate of resistance to the anti-staphylococcal hemi-synthetic penicillin (MRSA and MRSE) is constantly increasing during the last decade[14], reaching 18% and 40% respectively.

Enterococci[14] (that are not classified to streptococci but have been promoted to a separate genus) are responsible for approximately 6% of NVEs. They form part of the normal flora of the gastrointestinal tract and the urethra. Typically, high doses of penicillin combined with aminoglycoside are required in order to achieve synergy[2,14].

1α. ***Intravenous drug addicts***[2,6] form a special NVE subgroup. They cover 8% or even more[9] of IEs, while the incidence of the disease in drug addicts is believed to be 100-1000 times higher than in the general population[15]. They are usually young men without pre-existing valvulopathy, which explains why there are no heart murmurs. Pathogens usually come from the skin or from infected narcotic substances or syringes, while the right cavities are mainly affected (>50%) (tricuspid valve). Due to the involvement of the tricuspid valve, septic emboli affect the lungs and the disease may manifest as pneumonia. The main causative pathogen (60%) is Staphylococcus aureus. In general, the clinical course is good but it is characterized by high recurrence rates, mainly due to the continuous use of drugs. Increased blood oxygenation in the left cavities (leading to higher microbe proliferation) and better penetration of antibiotics in vegetations of the right cavities may be responsible for the better course of the right-sided IE compared to left-sided IE.

2. **PVE**. Prosthetic valves, as foreign bodies, predispose to endocarditis. The incidence of IE in individuals with prosthetic valves is 1-4%[2].

Conventionally, PVEs are divided into **early**, when they are manifested within 2 months following valve replacement, and **late**, when they are manifested 2 months or later following valve replacement[2,3,6,7,13,16]. However, since the IE onset cannot be determined accurately, many authors consider early PVE the disease that occurs within the first 12 months following replacement[17]. Early PVE reflects, in general, an infection during the peri-operative period and is due to staphylococcus in 50% of the cases, particularly *S. epidermidis*, that has the ability to become attached to foreign bodies[13,16]. Late PVE occurs following valve epithelisation, its pathogenesis and microbiology resembling to the ones of NVE, since it is due to transient bacteremia[2,13].

There seems to be no difference in IE incidence among mechanical and bioprosthetic valves[2].

3. **Pacemaker endocarditis** (PE)[18-23] is a new clinical entity. It is an infection of the endocardial electrode of the permanent pacemaker and is a rare but severe complication of artificial pacing of the heart. It is similar to early PVE, since it is considered to be due to an infection during the pacemaker implantation period or to the subcutaneous im-

Table 1. Endocarditis pathogens based on cultures (blood/tissue/material cultures) and *serum reactions[12].

Isolated microbes	Number of strains				
	Native valves	Prosthetic valves	Pacemaker	Total	%
Streptococcus viridans	17	2	–	19	19,4
Other streptococci	2	–	–	2	2,0
Staphylococcus aureus	11	2	6	19	19,4
Staphylococcus epidermidis	7	5	4	16	16,3
Enterococcus spp.	3	–	–	3	3,1
HACEK group	1	1	–	2	2,0
Enterobacteriacaceae	1	1	1	3	3,1
Pseudomonas spp.	–	2	–	2	2,0
Acinetobacter calcoaceticus	1	–	–	1	1,0
Campylobacter sp.	–	1	–	1	1,0
Corynebacterium sp.	–	1	–	1	1,0
*Brucella melitensis**	2	–	–	2	2,0
*Coxiella burnetii**	1	–	–	1	1,0
*Listeria monocytogenes**	–	1	–	1	1,0
Propionibacterium acnes	–	1	–	1	1,0
Candida spp.	3	2	–	5	5,1
Aspergillus sp.	1	–	–	1	1,0
Negative cultures / serum reactions	7	11	–	18	18,4
Total	57	30	11	98	100

plantation of the battery and not to transient bacteremias, since the wire is later covered by fibrous tissue that renders difficult the attachment of microbes during transient bacteremias. The main cause (>50%) is *Staphylococcus epidermidis*, that is attached to foreign bodies. Chemoprophylaxis during pacemaker implantation seems to reduce PE risk[24], but this has not been widely established.

It should also be noted that in PVEs and PEs, the rates of penicillin resistant staphylococci are double those in NVEs[14], reaching 38% and 78% for MRSA and MRSE, respectively[12]. This makes sense if we consider the infection pathway (community-acquired microbes / hospital strains) in the two cases.

Currently, with the recent microbiological techniques regarding cultures and serum reactions, we admit that practically **any microbe** may cause endocarditis[1,2,6,25]. The microbes that have been considered culprits in a recent multicentric study in the Greek population[12] are shown in table 1.

HACEK group microorganisms[14,25,26] (*Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp., *Kingella kingae*) are responsible for 2-5% of IEs. They are part of the normal mouth flora, they cause a sub-acute clinical image and are difficult to isolate in blood cultures, since they are slow to develop and need prolonged incubation.

Streptococcus bovis is related to polyps or cancerous lesions of the intestine[1-3].

Fungal endocardites[1-4,25] are characterized by large vegetations and high mortality rates. The most common causes are *Candida albicans* and *Aspergillus* spp. They are responsible for approximately 5% of endocardites and, in general, predisposing factors are reported (prolonged hospital stay, intravenous central catheters).

Pathogenesis - predisposing factors

Three hemodynamic factors are predisposing to IE development[2,7]:
– rapid blood flow (jet)
– flow from a cavity with high pressure to a cavity with low pressure (shunt)
– narrowed opening that divides two cavities so as to create pressure gradient

IE lesions tend to be created immediately behind the opening with stenosis, however, satellite lesions may also be created where the blood jet hits the endocardium. For example, in mitral valve regurgitation, lesions appear in the atrial surface of the valve and the atrial wall across the valve.

During the intense flow that is created, the valve loses its endothelium since it is removed by the blood jet. In this site, fibrin and platelets are aggregated, thus creating sterile vegetations. IE is induced when, during transient bacteremia, microorganisms colonize these sterile vegetations. Later on, on top of the microbes, new fibrin and platelets aggregates are deposited, creating protected "niches" of microbes, which the phagocytes of the body's defense system cannot easily penetrate. Thus, recent vegetations consist of microorganisms, fibrin, platelets, red blood cells and white blood cells. Following treatment, the invasion from leucocytes and fibroblasts leads to fibrosis and scarification in the valve, some times with hyalinization and calcification and, consequently, stenosis or failure[2,6].

A necessary condition for the induction of IE is transient bacteremia[2]. This could be **traumatic** (when areas with microbial flora are injured, such as the oral cavity, the lower gastrointestinal tract, the urogenital system or the skin) or **non traumatic** (as in skin or lung infections). With regard to traumatic bacteremia, dental procedures constitute the most common entrance of microbes. The association of dental procedures with IE is already known since in 1909, when Horder observed that there is an association between "streptococcus viridans" in the oral cavity and IE in patients with heart diseases[27]. Yet, other surgical procedures, such as urological, gynecological, lower gastrointestinal tract endoscopic or surgical procedures may also lead to IE. Bacteremia is caused by microbes of the respective flora of the traumatized region: in dental procedures, it is usually caused by Streptococci viridans, in skin trauma by Staphylococcus, while in the remaining cases, it is usually caused by enterococcus and Gram (–) bacteria.

It is also worth mentioning that traumatic bacteremia can also be caused by trivial daily life events, such as the intense brushing of teeth and mastication of hard food (incidence of bacteremia 25% and 38%, respectively, quite significant compared to 40% of bacteremia caused by tooth extraction)[2,6,27]. This explains why in a significant proportion of IE due to oral cavity microbes, there is no mentioning of a dental procedure. Traumatic bacteremias, however, are transient, they last approximately 15-30′ and usually the number of circulating microorganisms is low (<10/ml of blood), explaining why persons with normal valves do not manifest any problems.

Clinical manifestations - laboratory and paraclinical findings

Signs and symptoms of IE are due to 4 factors:
– local endocardial infectious procedures
– aseptic or septic emboli from vegetation debris that may literally affect all organs
– continuous bacteremia with microbes diffusion to distal foci and
– development of immune complexes.

The symptoms[2,6] generally appear within two weeks from the transient bacteremia. If the microorganism presents low virulence, such as Streptococcus viridans, the disease starts with non specific symptoms, such as malaise, anorexia, night sweats and loss of weight. If the microbes present high virulence, such as staphylococcus aureus, the onset of the disease is very precipitous.

Fever is present in almost all the patients, aside from the elderly or individuals who have recently taken antibiotics. Usually, it does not exceed 39˚C and is relatively well tolerated. **Heart murmur** is present in most of the cases, apart from right cavity IEs in drug addicts and from the initial phase of acute IE. According to currently valid Durack criteria, a pathognomonic (major) criterion is considered to be the newly appearing regurgitation murmur that is, however, difficult to verify. **Splenomegaly** also appears, usually painless, unless there is an embolus or an abscess. **Arthralgias**. Skin manifestations: Striated subungual hemorrhage (non specific), Janeway lesions (painless erythematous lesions on the palms or soles, due to septic emboli), Osler nodes (sensitive nodes of autoimmune etiology, similar to rheumatic nodes). **Roth spots** on the retina (egg-shaped hemorrhages with a luteal centre, near the optic nerve). **Embolic episodes**[4] are present in 25%-50% of patients and may occur during treatment and/or after treatment. In left cavities IE, they mainly affect the brain in the form of vascular cerebral episodes and, less commonly, in the form of abscesses or purulent meningitis. They are less common in the spleen, the kidneys, the liver or the limbs. In right cavities IE (drug addicts), septic emboli in the lungs are present at very high rates (70-100%). **Circulatory system manifestations**[4]: congestive heart failure (due to valve destruction), myocardial infarction (due to coronary embolism), conduction disturbances (due to abscess or extension of the inflammation). Renal disease, in the form of glomerulonephritis from immunocomplexes

(up to 80%) due to high antibodies titers, or infarctions or abscesses.

In common laboratory examinations[2,6], normocytic, normochromal anemia with or without leucocytosis may be present as well as microscopic hematuria with or without albuminuria. Among inflammation and immunological reaction indices, sedimentation rates and CRP are increased, Ra-test is often positive and the complement is reduced.

Blood cultures[1,2,4,6] are positive in 90-95%[10,26] of patients who have not received antibiotics. Bacteremia is continuous, meaning that no planning of the sampling in accordance with fever is necessary. Blood samples for culture (usually 3) must be taken in intervals of ≥30′ to prove the continuity of bacteremia, only one sample must be taken in each venipuncture, the sample must be incubated in both aerobic and anaerobic vessels and it must be followed for at least 3 weeks, to increase the possibilities of development of difficult to develop microorganisms. Blood cultures may be negative in case of use of antibiotics (although retins are used today that absorb antibiotics[27]), in fungal IE (Candida / Aspergillus) or Coxiella burnetii (Q fever). **Serum reactions** help in certain cases, such as in Q fever mentioned above, Brucella, Chlamydia, Legionella and Bartonella[4].

Echocardiography may reveal vegetations.

Echocardiography, the transthorasic (TTE) and much more the transesophageal one (TEE) that has been added in the last few years, currently constitutes a major diagnostic technique, both for the confirmation of IE diagnosis and for taking of therapeutic decisions. TEE has significantly increased the sensitivity of the method in discovering small vegetations (95% vs. 70%)[2], in IE of prosthetic valves (82% vs. 36%)[2], in pacemaker endocarditis (95% vs. 23%)[18-20] and in the imaging of para-valvular abscesses (90% vs. 28%)[1]. Echocardiography should be performed on clinical suspicion of the disease, even when the blood cultures are negative, to be used, among others, as a baseline for eventual future findings. This is why, although the TTE is executed first due to ease and to the fact that no special device is needed, in case of negative TTE result, TEE should be performed. In case of serious IE Suspicion, and even on the ground of negative TTE, the examination should be repeated.

It should be noted that echocardiography does not establish a causative diagnosis and that its determination requires clinical or microbiological verification. Infective vegetations can neither be distinguished between thrombi, pannus or lesions of the native valves, nor is it possible to distinguish from active and healed vegetations[28]. Furthermore, thickening, nodules, small calcifications of native valves may be erroneously interpreted as vegetations.

Following effective antimicrobial treatment, vegetations disappear in 29% of cases, while they remains unaltered in 58%, in 24% are reduced and in 17% are increased. Consequently, changes in vegetation must be interpreted within the clinical context, since they do not reflect the efficacy of treatment[29] per se.

The extension of the infection to the valve neighboring tissues may lead to the formation of abscesses, Valsalva sinus aneurysms, intracardial fistulae and purulent pericarditis. TEE with its high sensitivity is a valuable means for the diagnosis of such lesions[30].

Pooled studies data converge to the conclusion that vegetations >10 mm present a double embolism risk (40% vs. 20%). The risk is even higher when they affect the mitral valve and when they are mobile[31].

Finally, in right sided IE, the imaging of vegetations has been associated with prolonged fever during treatment and an increase of the right ventricle dimensions. The above is not proportional to the size of vegetations, nor is the presence and the size of vegetations a prognostic factor for the failure of treatment or for the need of surgical intervention[32].

Diagnosis

IE must be included in differential diagnosis of:
– febrile condition (>1 week) in patients with heart murmur
– febrile condition in intravenous drug addicts
– febrile condition in patients with prosthetic valves
– young patients with a sudden neurological event.

In 1994, David Durack et al published in the *American Journal of Medicine,* the proposed new criteria (Duke criteria) for IE diagnosis[26], that subsequently replaced the older von Reyn et al criteria (Beth Israel criteria) since 1981[33]. These are also currently valid, unaltered, although certain modifications are considered[4], by the same group of Duke university[34].

Durack extended the diagnosis of definite IE cases, apart from cases based on histopathology

criteria (samples from surgery or autopsy), to cases of clinical data fulfilling the 2 major criteria, as defined by him, or 1 major and 3 out of the 6 minor criteria, or simply 5 minor criteria, while he abolished the term "probable" that existed in the von Reyn criteria. Possible cases are considered those that do not fulfill the criteria of the definite IE but are not rejected either. Rejected are those cases where there is: a) definite differential diagnosis, b) recession of the manifestations when antibiotics are administered ≤4 days, or c) in absence of histopathological documentation of IE on surgical or autopsy samples, following antimicrobial treatment ≤4 days. The novelties that Durack introduced were echocardiography and the use of intravenous drugs.

More analytically, the **major criteria** include:
1) typical blood culture (typical microorganism or continuous bacteremia), and
2) positive echocardiography (mobile intracardial morpheme, abscess or prosthetic valve dehiscence, or auscultation findings of a new valve failure murmur (and **not the change** of the murmur).

Minor criteria include:
1) predisposing factors: valvular lesion, prosthetic valve or intravenous drug use
2) fever ≥38°C
3) vascular phenomena: emboli (septic or not), Janeway lesions
4) immunological phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
5) indicative microbiological findings: positive blood culture that does not meet the major criterion (e.g. 1 positive blood culture), serum indication of active infection
6) indicative ultrasound findings, that do not meet the major criterion (e.g. non mobile mass, thickening or perforation of the cuspids).

It is also mentioned, for further clarification, that the following are considered typical microorganisms: Streptococcus viridans, *S. bovis*, HACEK group, *Staphylococcus aureus*, Enterococcus**, for which 2 positive cultures are enough, whereas continuous bacteremia is documented with positive blood cultures at intervals of 12 hours or 3 or more blood cultures with an interval of at least one hour the first from the last.

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* For S. aureus and enterococcus the following restrictions are valid: 1) to be community acquired and 2) to prove absence of an alternative infection focus.

In particular *Staphylococcus epidermidis* is not considered to be a typical microorganism, since it often causes contamination of the blood cultures. In order for the major criterion to be met, continuous bacteremia must be proven from this microbe, while one positive blood culture does not befall on the 5th minor criterion.

For PE, Klug et al[18] propose the respective adjustment of the Durack criteria.

Treatment

The main therapeutic principles[2] are the following:
– Parenteral administration of antibiotics, in high doses and long duration. Microbes in the vegetations are in high concentrations and they are protected by the body's defense system. Consequently, high levels of antibiotic must be attained for a long period of time.
– The sensitivity of the responsible microorganisms is accurately determined. Thus, in isolated microorganisms, the sensitivity must be accurately determined together with the Minimum Inhibitory Concentration (MIC) in the antibiotics that are usually administered.
– All definite IEs according to Durack must be treated with drugs. As far as the possible cases are concerned, the decision for the treatment administration or not is individualized[26] and lies at the discretion of the clinician[34].
– If the patient is in critical condition, empirical treatment based on epidemiological data is administered, immediately after the receipt of 3 blood cultures within a one-hour period. The treatment will be modified later, in accordance to the laboratory results.
– If the patient's condition allows it (subacute IE), the treatment will be delayed until laboratory documentation of the cause.

Antimicrobial treatment (Table 2) usually administered for the most common pathogens (streptococcus / staphylococcus / enterococcus / HACEK group), has been determined by Consensus of the American Heart Association (AHA), already since 1995[14]. In summary, in most of the cases, intravenous treatment is administered initially, for 4-6 weeks, in combination with b-lactame or glycopeptide and aminoglycoside, in accordance with the antibiogram, adding per os rifabicin in staphylococcal endocarditis of the prosthetic valves. The same consensus committee refers to the therapeutic management of the

Table 2. Pharmacological treatment of endocarditis (Sanford Guide to Antimicrobial Therapy 2000, 30th edition, modified).

	Suggested treatment	
	First choice	**Second choice**
A - Native valves		
Empirical treatment before blood culture results	Penicillin G 20 million U or ampicillin 12 g i.v. daily (continued infusion or in 6 doses) + oxacillin 2 g / 4 h i.v. + gentamicin 1 mg/kg /8 h i.m. or i.v.	Vancomycin 15 mg/kg** /12 h i.v. + gentamicin 1 mg/kg/8h i.m. or i.v.
Positive Blood Cultures		
- *Streptococcus viridans, S. bovis*	Penicillin G 12-30 million U. for 2-6 weeks*** or ampicillin 12 g i.v. daily for 4-6 weeks (continued infusion or in 6 doses) + Gentamicin 1 mg/kg/8h i.v. for 2-6 weeks	Vancomycin 15 mg/kg**/12h i.v. With or without*** gentamicin 1 mg/kg /8h i.v. for 4-6 weeks
- Enterococci penicillin-sensitive	Penicillin G 18-30 million U. *** or anpicillin 12 g i.v. daily (continued infusion or in 6 doses) + gentamicin 1 mg/kg /8h i.v. for 4-6 weeks	Vancomycin 15 mg/kg**/12h i.v. + gentamicin 1 mg/kg /8h i.v. for 4-6 weeks
- Enterococci penicillin-resistant	Vancomycin 15 mg/kg**/12h i.v. + gentamicin 1 mg/kg/8h i.v. for 4-6 weeks	
– *Staphylococcus aureus* methicillin -sensitive (MSSA)	Oxacillin 2 g / 4h i.v. for 4-6 weeks + gentamicin 1mg/kg /8h i.v. for 5 days	Vancomycin 15 mg/kg**/12h i.v. for 4-6 weeks
– *Staphylococcus aureus* methicillin-resistant (MRSA)	Vancomycin 15 mg/kg** /12h i.v. for 4-6 weeks	
– HACEK group	Ceftriaxone 2 g daily i.v. for 4 weeks	Ampicillin 12 g i.v. daily (continued infusion or in 6 doses) + gentamicin 1 mg/kg /8h i.m.or i.v. for 4 weeks
B - Prosthetic valves		
Empirical treatment before blood culture results	Vancomicin 15 mg/kg** /12h i.v.+ gentamicin 1 mg/kg /8h i.v. + ryfampin 600 mg daily per os	
Positive Blood Cultures		
– *Staphylococcus epidermidis*	Vancomycin15 mg/kg** /12h i.v.+ ryfampin 300 mg /8h per os for 6 weeks + gentamicin 1mg/kg /8h i.v. for 2 weeks	
– *S. aureus* methicillin-sensitive (MSSA)	Oxacillin 2 g / 4h i.v. + ryfampin 300 mg /8h per os for 6 weeks + gentamicin1mg/kg /8h i.v. for 2 weeks	
– *S. aureus* methicillin-resistant (MRSA)	Vancomycin 1 g** /12h i.v.+ ryfampin 300 mg /8h per os for 6 weeks+ gentamicin 1mg/kg /8h i.v. for 2 weeks	
– *Streptococcus viridans*, enterococci	As for native valves	
– *Fungi (Candida, Aspergillus)*	Amphotericin B i.v. + fthoriocytosine per os or azole (e.g. fluconazole i.v.) for total duration >3 months	

  *It is preferable to wait the blood culture results, unless the patient is in bad clinical condition or in severe heart failure. The empirical treatment is modified later according to blood culture results.

  ** Pressumption: clearance creatine ≥80 mL/min

*** Depends on MIC

less common causes[4]. Liposome amphotericin is administered in fungal endocarditis, alone or in combination with fluorocytosine or fluoconazole, while in the rest of the endocarditis cases (Brucella, Legionella, Listeria, Q fever, etc) specialized treatment is administered. In most of the above cases, intravenous administration is followed by per os administration for a total of more than 3 months, which becomes indefinite for Q fever and fungal endocardites. In cases of inability to isolate the pathogen, empirical treatment is used, taking into consideration the epidemiological evidence. There are conflicting views, but usually high penicillin G doses are administered with or without anti-staphylococcal

penicillin. Alternatively, vancomycin for 6 weeks with addition to the scheme of gentamycin for the first two weeks[3,13] may be used.

Currently, we have accepted the role of early cardiosurgical intervention in case of heart complications (such as congestive heart failure), intracardial abscesses, failure of antimicrobial treatment and fungal endocarditis[1-4,13]. Regarding PVE, many studies have shown that the timely replacement of the affected valve contributes to significantly lower mortality rates compared to conservative treatment alone[16]. Particularly in cases of *Staphylococcus aureus* infection, due to the aggressiveness of the disease, the replacement of the affected valve is not exclusively considered only in cases with indications of heart complications[1,17]. Also, in PE cases, we have established the value of removal (intravascular or thoracosurgical) of the whole pacemaker system, as soon as possible[18-23].

Prognosis

In most of the patients, body temperature returns to normal within 3-5 days from the onset of treatment[2]. However, complications such as emboli or congestive heart failure may be manifested later, during or even after the end of treatment[2,6,14].

Mortality rates in general[8,9,12,26] range between 9% and 36%. Mortality rates in PVE are significantly higher (25%-30%)[12,16,17], as are in the case of *Staphylococcus aureus* IE (25-40%)[14,17] (excluding drug addicts, with a mortality rate <10%). In case of PVE and *S. aureus* combination, mortality range climbs to 28%-82%[17]. In PE, mortality rates range from 24% to 27%[18,20]. The conservative treatment, at least in PVE, is followed by significantly higher mortality rates versus surgical treatment[2,7,12,16,17]. Re-infection or recurrence in IE is reported in 6-15% of cases[10,12,26].

Prophylaxis

Indirect indications suggest that chemoprophylaxis reduces the risk of IE, prohibiting the blood circulating microbes to infect the endocardium, during the transient bacteremia interval[2]. This occurs via 3 mechanisms: destruction of microbes in blood, prohibiting their attachment to the valves and inhibition of their proliferation on the valves[27].

The questions that arise for the clinician are as follows:

– which patients benefit from prophylaxis?
– in which medical conditions?
– which antimicrobial regimen is the most effective?

The American Heart Association (AHA, 1997)[35] divided patients into high, moderate or negligible risk groups. It is believed that the first two categories should undergo chemoprophylaxis, while the risk for the third category is considered the same with the rest of the population. The **high risk** group includes, among others, patients with prosthetic valves or a previous IE event. In the **moderate risk** group the acquired valvulopathies are included. In the **negligible risk** group patients with a pacemaker are included. Especially for *mitral valve prolapse* what is worth noting, is that it is included in the negligible risk group, when it is not accompanied by valvular failure (no chemoprophylaxis is administered). This is included in the moderate risk group, when it is accompanied by failure or thickening of the cuspids (then chemoprophylaxis is administered). In case of suspicion of prolapse, if the presence of regurgitation cannot be determined with auscultation and/or echocardiography, chemoprophylaxis is administered.

Also, AHA determines more accurately the actions for which chemoprophylaxis is indicated or not. As far as **dental procedures** are concerned, prophylaxis is administered in general in procedures associated with gingival or mucosa bleeding. In cases of unpredicted hemorrhage, animal models have shown that antibiotics administered within 2 hours from the intervention is efficient[27]. With regard to **other medical procedures** it is notable that among those where chemoprophylaxis is not necessary caesarian sections, heart catheterization and implantation of a pacemaker are included.

The selection of **antibiotics** is based on the type of microbes that usually cause bacteremia. Thus, in dental procedures, prophylaxis aims at streptococci viridans, while in procedures of the lower gastrointestinal and urogenital tract, the antimicrobial regimen targets enterococcus. AHA have simplified chemoprophylaxis to dental or bucal cavity procedures to *2 gr of amoxicilin per os 1 hour before the surgery* and have abolished the second dose, while as an alternative they consider clindamycin instead of erythromycin. For lower gastrointestinal or urogenital tract surgical procedures, the schemes have been simplified to ambicilin and gentamycin in the high risk group and only ambicylin or amoxicylin in the moderate risk group of patients.

Approximately the same are indicated by the European Consensus (Consensus, 1995)[36], having remained to 3 gr of amoxicilin one hour before the procedure (the second dose has also been abolished) here.

As far as *permanent pacemakers* are concerned, although the implantation and existence of the pacemaker does not befall the prophylaxis categories, in a meta-analysis[24] it was shown that chemoprophylaxis in implantation reduces the incidence of serious infectious complications. In practice, the administration of antibiotics targeting staphylococcus during pacemaker implantation is widely used.

In individuals with IE risk factors, emphasis is given to regular dental examinations for the best possible *hygiene of the oral cavity* in order to minimize potential bacteria sources[35].

There is also skepticism with regard to the efficacy of chemoprophylaxis. Van der Meer et al[37] have found that only 13% of the individuals with predisposing factors that are subject to surgical procedures, will develop IE and that in these individuals chemoprophylaxis does not guarantee IE prevention, since the protection it provides accounts for 49%. Thus, theoretically speaking, the administration and full compliance with chemoprophylaxis could prevent IE only in 6% of the cases. Lacassin et al[38] are also driven at the same rate (5-10%), who, as Strom and colleagues[10], question the significance of most dental procedures as risk factors for induction of IE, transferring the greatest weight to surgical operations.

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