# ETIOLOGY AND INCIDENCE OF INFECTIOUS DISEASES OF THE HEART. AN UPDATE

**Irina Alina Cucu[1,2], Mariana Carmen Chifiriuc[1,2*]**

[1]*University of Bucharest, Faculty of Biology, Microbiology Immunology Department, Bucharest, Romania*
[2]*The Research Institute of the University of Bucharest, Bucharest, Romania*

**ABSTRACT**

**Introduction**: Cardiovascular diseases (CVD) rank first among the mortality causes at a global scale. According to the World Health Organization (WHO), 24.2 million people are likely to die from this disease by 2030, representing 32.5% of all causes of death. Although in recent years new methods of treating and diagnosing CVD have been discovered, the main treatments still involve surgery and the use of cardiac devices, maneuvers associated with a high risk of infection.

**Objectives**: The purpose of this paper was to review the main etiological agents of heart infections, as well as their incidence and contribution to the morbidity and mortality rate in CVD patients.

**Methods**: Data was searched and extracted from published literature using PubMed, ScienceDirect and Elsevier databases.

**Results**: Different viral, bacterial, fungal and protozoa pathogens can specifically infect the endocardium, pericardium and myocardium, respectively, the etiology depending on the geographical area, the immune status of the patient and comorbidities.

**Conclusion**: With the increasing prevalence of CVD, the risk of infection is also on the rise, due to the aging of the population, associated with a growing rate of cardiac surgery and use of cardiac devices, the presence of various pathologies such as HIV infection, diabetes, renal failure, autoimmune disease, and coronary heart disease (CHD). For an efficient management of patients with heart infectious diseases, more epidemiological studies should be done in different geographical areas to determine the incidence of the etiological agents of infectious pericarditis, endocarditis and myocarditis, respectively.

**Keywords**: cardiovascular disease, endocarditis, myocarditis, pericarditis, heart infection

**REZUMAT**

**Introducere**: Bolile cardiovasculare reprezintă principala cauză de mortalitate la nivel global. Conform Organizației Mondiale a Sănătății (OMS), sunt estimate 24.2 milioane de decese datorate acestei patologii până în anul 2030, reprezentând un procent de 32.5% din totalul cauzelor de mortalitate. Deși în prezent s-au înregistrat progrese importante în diagnosticarea și tratarea bolilor cardiovasculare, intervențiile chirurgicale și utilizarea dispozitivelor cardiace reprezintă unele dintre cele mai utilizate proceduri pentru tratarea acestei patologii, ambele asociate cu un risc ridicat de infecție.

**Obiective**: Obiectivele acestui articol sunt stabilirea principalilor agenți etiologici implicați în infecțiile cardiovasculare, precum și a incidenței și contribuției acestora la rata de mortalitate și morbiditate a pacienților cu patologie cardiovasculară.

**Metode**: Datele utilizate au fost obținute prin studiul literaturii medicale publicate în PubMed, ScienceDirect și Elsevier.

**Rezultate**: Diverși patogeni, precum bacterii, virusuri, fungi și protozoare pot infecta endocardul, pericardul sau miocardul, etiologia infecțiilor depinzând în principal de aria geografică, de statusul imun al pacientului și de prezența altor comorbidități.

**Concluzii**: Odată cu creșterea incidenței bolilor cardiovasculare, crește și riscul infecțiilor asociate, factorii favorizanți fiind îmbătrânirea populației, asociată cu un număr ridicat de intervenții chirurgicale și utilizări ale dispozitivelor cardiace, prezența diverselor patologii, precum infecțiile HIV, diabetul, bolile autoimune, insuficiența renală și malformațiile congenitale cardiace. Pentru managementul eficient al pacienților cu infecții cardiace, sunt necesare studii epidemiologice realizate în diferite zone geografice, pentru a stabili incidența agenților patogeni implicați în pericardita, endocardita și miocardita infecțioasă.

**Cuvinte-cheie**: boala cardiovasculară, endocardită, miocardită, pericardită, infecție cardiovasculară

**Corresponding author:* Mariana Carmen Chifiriuc, University of Bucharest, Faculty of Biology, Microbiology Immunology Department and the Research Institute of the University of Bucharest, Bucharest, Romania; e-mail: carmen.chifiriuc@gmail.com

## INTRODUCTION

From the uncovering of atherosclerosis in Egyptian mummies, dated 3.500 years ago, cardiovascular diseases (CVDs) still remain one of the greatest challenges for clinical medicine, concerning both diagnosis and treatment [1, 2]. The discovery of antibodies, antigens, blood typing and immunosuppressant treatment, made heart transplant a viable solution. Nowadays, we can use CRISPR-Cas9 for genome editing, while nanotechnology provides novel biomarkers for CVDs patients diagnosis and treatment. Also, 3D printing and computational fluid dynamics (CFD) can facilitate high precision surgery techniques [3-7].

But, despite the tremendous progress that has been made, CVDs are still posing a great threat to human health, with an estimated number of 17.6 million deaths in 2016 (Fig. 1) and of 24.2 million by 2030.

Simultaneously with the extending number of CVDs, the risk of infections rises proportionally. Each layer of the heart could represent an entry gate for microorganisms that can cause specific infections, known as infective endocarditis (IE), myocarditis and pericarditis, respectively. The incidence of these infections is increasing due to different factors. The aging population requires more surgical procedures for valve replacement (almost 30% of patients that suffer from endocarditis have prosthetic valves) and the use of ventricular assist devices (a growing rate of 23% per year). In 2010, 5% of the CVDs patients required heart transplants, a percentage that is growing year by year. Other illnesses such as HIV infection, diabetes, renal failure, co-occurring with invasive procedures such as tooth extraction, piercing, and catheterization, can represent means of entry for pathogens that can end up in the systemic circulation [9 - 11].

According to the World Health Organization (WHO), in 2015 there were 413,332 deaths reported due to endocarditis, myocarditis and cardiomyopathy, representing 2.34 % of the total number of deaths due to CVDs (Fig. 2), with a slight increase in 2016, i.e. 435,500 deaths (2.47%).

## INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) is defined as an inflammation of the endocardium, being characterized by the development of a vegetation composed of microorganisms, fibrin, inflammatory cells and platelets. IE is a potentially fatal disease, with an estimated mortality rate of 20% in the case of nosocomial IE, with the first year after hospital discharge having the highest mortality, reaching 40%. Its incidence is estimated at 6-7 cases per 100,000 in developed countries and up to 6-10 cases per 100,000 in developing countries. At first, infective endocarditis was classified as subacute, acute and chronic. Currently,

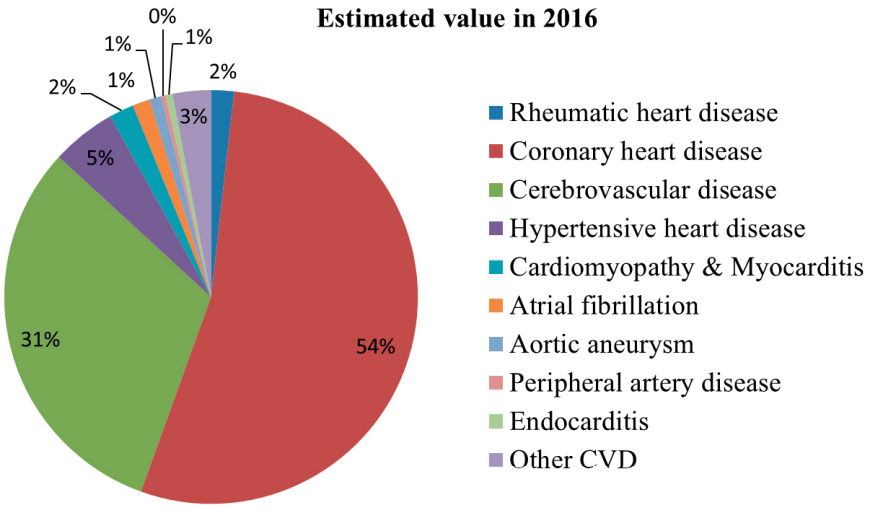


**Fig. 1. Estimation of deaths due to CVDs in 2016 (Deaths and Disease Burden by Cause: Global Burden of Disease Estimates for 2016)** [8]

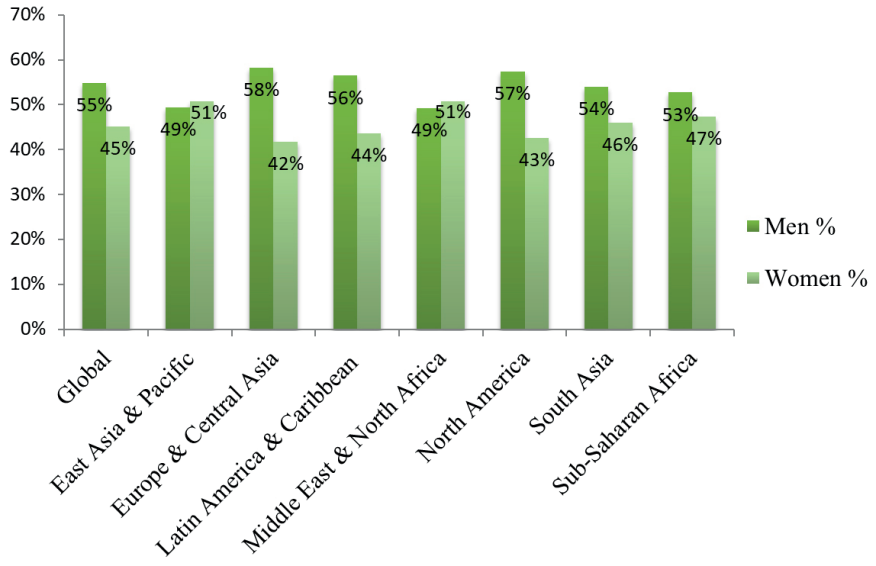


**Fig. 2. Percentage distribution of mortality rate by endocarditis, myocarditis and cardiomyopathy of the total number of deaths due to cardiovascular infections in each of the seven world regions, in 2015, calculated by the analysis of the data reported by WHO**

this classification is no longer valid because describing the source of infection is more helpful in clinical setting [12-16].

Patients who went through surgical procedures are more prone to infections. They should follow certain guidelines regarding diet, teeth hygiene and tooth extraction, in order to prevent an infectious episode. High or low concentrations of Fe, Mn and Zn, can be linked to infections [13, 17]. Likewise, a higher risk is seen in patients who suffer from illnesses such as HIV infection, diabetes, Whipple disease (17-55% have cardiac implication, that may involve the myocardium/endocardium/pericardium) or hypereosinophilic syndrome (known as Loeffler's endocarditis, 60% of the cases with cardiac involvement) [18, 19].

IE can have bacterial, viral or fungal etiology. Viral endocarditis is considered to be more of a dissemination of the virus originating from another site. Older studies suggest that viral endocarditis can be caused by Coxsackie virus in monkeys, encephalomyocarditis virus in mongooses and Virus III in rabbits. Whilst their action results in inflammatory reactions, there is a substantial uncertainty regarding their presence in the human endocardium. For example, IE attributable to Cytomegalovirus (CMV) is more secondary to viremia, the primary CMV infection being probably due to other different pathologies seen in the respective patients, such as HIV, hepatitis B, and drug use [20 - 22].

Fungal endocarditis is a rare disease, with a low incidence in comparison to bacterial endocarditis (between 1 to 10%). From a clinical point of view, it is the most life-threatening form of endocarditis, with a mortality of 50%, diagnosis being made in most cases post-mortem. Fungal endocarditis damages native and prosthetic valves (2-10% incidence), other cardiac devices (35-39%) and the surface of the endocardium. As a result of the increased use of cardiac devices, a growth in the occurrence of fungal pathogens is expected [23-26].

The most widely spread pathogens are *Candida* sp. (50-60%) and *Aspergillus* sp. (20-25%) (Table 1). The prevalence of fungal etiological agents is influenced by the state of the patients (immunocompromised, HIV positive, undergoing surgery, with parenteral nutrition, drug abuse, prolonged use of antibiotics, congenital heart defects, long term use of cardiac devices), environmental factors being equally important (hospital, hygiene, atmosphere). Thereby, endocardial infections with *Candida* sp. are connected to hospital environment, while *Aspergillus* sp. can accompany cardiac

**Table 1. Etiological agents of fungal endocarditis** [23-27]

| Etiological agents | Fungal Endocarditis |
|---|---|
| *Candida* sp. | *Candida albicans*<br>*Candida glabrata*<br>*Candida tropicalis*<br>*Candida parapsilosis* |
| *Aspergillus* sp. | *Aspergillus fumigatus*<br>*Aspergillus flavus*<br>*Aspergillus niger*<br>*Aspergillus terreus* |
| Other | *Mucor* sp.<br>*Histoplasma* sp.<br>*Blastomyces* sp.<br>*Cryptococcus* sp.<br>*Trichosporon* sp.<br>*Pseudallesheria boydii*<br>*Scopulariopsis* sp. |

surgery [27, 28]. Identification of *Candida* sp. occurs in approximately 45-50% of cases [29, 30].

Bacterial endocarditis is the most common form of IE, staphylococci and streptococci being the most frequent etiological agents isolated in clinic [31]. Table 2 presents both etiological agents of IE and their incidence.

In the past, streptococci represented the main agents involved in bacterial endocarditis, due to the high incidence of rheumatic heart disease. Currently, *Staphylococcus* sp. is the main cause of this type of endocarditis. This changing epidemiology comes as a result of population aging (the elderly are more prone to infections by 4.6 times as compared to the rest of the population), the presence of HIV infection, diabetes, cancer, medical devices frequently colonized by coagulase-negative staphylococci (CoNS), but also because of the high occurrence of congenital heart defects (CHD) [42 - 44]. Those who suffer from CHD, especially men that have injuries on the left side of the heart, are more predisposed to endocarditis (1.61 cases per 1,000 people). Thus, those who suffer from lesions on the right side of the heart, atrial septal defect (ASD) and persistent arterial duct (PDA) are less susceptible to infections. Adults who have bacterial endocarditis related to their CHD have a 4% rate of mortality [45, 46].

*Staphylococcus aureus* is the most dominant pathogen of bacterial endocarditis around the globe. Other etiological agents identified on all continents are viridans group streptococci (VGS), CoNS, *Enterococcus* sp. and *Streptococcus*

**Table 2. Etiology and incidence of IE** [32-41]

| Period of data collection | 1980-2001 | 2000-2014 |
|---|---|---|
| Number of cases | 675 | 12772 |
| Staphylococci (%) | 24.4 | 38.1 |
| Streptococci (%) | 37.3 | 17 |
| Enterococci (%) | 5 | 14.4 |
| Gram-negative bacteria(%) | 4.8 | 6.3 |
| Culture negative (%) | 13.3 | 19.6 |
| Other (%) | 6 | 1.3 |
| Fungi (%) | 2.8 | - |

*bovis*. The only continent that stands out by having a different etiology than all of the rest is Asia, where the main pathogens are VGS and *Streptococcus* sp., staphylococci occupying the last place, in terms of incidence. According to a study, rheumatic heart disease is the main contributor to this specific etiology of endocarditis in Asia (33-66%), a high mortality being present in South and East Asia. Furthermore, when compared to other continents, Asia has the highest occurrence of CHD (9.3 per 1,000 live births) [47-50].

Although the causative agents found in this pathology are common, other bacteria less typical can be clinically identified. For example, Gram-negative bacteria (incidence 1-3%) produce infections with a lower mortality in comparison to other bacterial pathogens. Mainly, they belong to the HACEK group (Acronym HACEK stands for *Haemophilus* species, *Aggregatibacter* sp., *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* sp.), *Enterobacteriaceae*, but also to species of *Pseudomonas* genus, predominantly *Pseudomonas aeruginosa*. Anaerobic bacterial cultures (2-16% cases of bacterial endocarditis) have been found in 20% of the cases in polymicrobial associations, affecting more men than women, with poor teeth hygiene. Even though they represent just 1% of pathogens, they still have a high rate of mortality, estimated at 21-43%. Polymicrobial endocarditis is rare, estimated at 1-6.8% and can be caused by pathogens ranging from CoNS, enterococci, anaerobic bacteria to Gram-negative bacilli and fungi. *Propionibacterium acnes*, *Lactobacillus* sp., *Clostridium* sp., *Peptostreptococcus* sp. and *Bacteroides fragilis* are the most frequently confirmed anaerobic pathogens [51 - 53].

Blood culture-negative endocarditis (BCNE) represents a tremendous complication in clinical setting and has a high incidence that ranges from 2.5% to 31%. BCNE appears in most cases due to antibiotic prophylaxis, but also from such causes as the existence of autoimmune diseases, uncultivable or intracellular bacteria [54, 55]. A number of fastidious pathogens are most frequently detected. *Tropheryma whipplei* is among them and is culture-negative in 40% of cases. Another fastidious pathogen is the nontuberculous mycobacteria - *Mycobacterium fortuitum*, *Mycobacterium chelonae*, *Mycobacterium abscessus* and *Mycobacterium chimaera* (a pathogen that contaminates the heater-cooler units used in cardiac surgery). Also, in this category we can find the HACEK group and *Abiotrophia defectiva*, a nutritionally deficient streptococcus that is responsible for 5% of all cases of endocarditis caused by streptococci. The most frequently identified pathogens of the BCNE etiology are intracellular pathogens, like *Legionella* sp. (nosocomial origin), *Coxiella burnetii* (3-5% of infective endocarditis, known to be the most severe form of Q fever), *Mycoplasma* sp. and *Chlamydia* sp. (only a few cases have been reported throughout the years) [56-60].

Based on the site of the infection, IE can be classified in left-side and right-side IE. Left-sided endocarditis (LSE) affects the aortic and mitral valve, being the most common in clinical setting and requiring in most cases surgical removal due to the possibility to cause heart failure in a short period of time. Right-sided IE involves the pulmonary and tricuspid valve. This type is occurring in just 5-10% of IE cases. Those who are at high risk for this pathology are intravenous drug abusers (30-40% of tricuspid valve endocarditis), have implanted medical devices or are undergoing certain procedures, such as dialysis. Also, there is a slight possibility to have more than one valve contaminated (17-22% of patients), i.e., from the most common to the most rare: aortic and mitral valve, mitral and tricuspid, aortic and tricuspid, aortic and pulmonary valve [61 - 63]. Table 3 enlists the incidence of infection taking into consideration the type of valves.

PVs represent a major risk factor of IE, particularly higher 6 months post valve replacement surgery. PV endocarditis (PVE) can have an early onset (in the first 2 months post-surgery) and is caused mostly by staphylococci (*Staphylococcus aureus*, *S. epidermidis)* or a late one (>2 months post-surgery), associated with enterococci.

Hospital acquired infective endocarditis (HAIE) has increased in the last decades and

**Table 3. The incidence of IE, according to the localization of the infection**

| Period of data collection | 1980-2001 [32-35, 64] | 2000-2014 [33, 37, 39] |
|---|---|---|
| Mitral valve (%) | 42.3 | 44.6 |
| Aortic valve (%) | 42.7 | 37 |
| Tricuspid valve (%) | 2.3 | 6.8 |
| Pulmonary valve (%) | 0.6 | 2.2 |
| PV (%) | 22.6 | 22.4 |

***Note:*** *PV = prosthetic valves*

affects the native valves in 54% of cases. HAIE is responsible for 20-34% of reported IE cases and is generally associated with virulent and resistant microorganisms, such as enterococci and methicillin-resistant staphylococci, generating high in-hospital mortality rates, of 27-38%. Determinants that are not supposed to be overlooked for this type of endocarditis are chronic hemodialysis, bacteremia with *Staphylococcus aureus* or methicillin-resistant *Staphylococcus aureus* (MRSA), ensuing a mortality of 10% at 30 days [65-68].

## INFECTIOUS MYOCARDITIS

Myocarditis is described as the inflammation of the myocardium and can be infectious and noninfectious (co-occurring with autoimmune diseases, or due to hypersensitivity to certain substances). It can have a fulminant or acute form. Infectious myocarditis (IM) has an unknown incidence, as a consequence of a long asymptomatic period, predisposing it to underdiagnosis. It affects mostly children and young adults. IM can be caused by viruses, bacteria and protozoa, the etiology being different depending on the geographical region. In developed countries viruses are mainly responsible for this pathology, while parasites (in particular, *Trypanosoma cruzi*, that causes Chagas disease) are the causal agents of infection in countries located in South and Central America. In 30-70% of cases, viral myocarditis leads to dilated cardiomyopathy (DCM), Coxsackievirus group B type 3 (CVB3) being the main responsible pathogen (in 50% of cases) [69-72]. The principal etiological agents responsible for IM are presented in Table 4.

The most widespread type of myocarditis is lymphocytic myocarditis; aside from this type there are two more types being mentioned: eosinophilic and giant cell myocarditis. The last form of myocarditis is accompanying autoimmune disorders (Kawasaki disease, disseminated lupus erythematosus, rheumatic fever, rheumatoid arthritis, etc.), while eosinophilic myocarditis can occur as a result of drug hypersensitivity or following smallpox and influenza vaccination [73, 75, 76].

Viruses are the main pathogens involved in IM. Until the 90's, Coxsackie B virus (CVB) had the highest prevalence, being presently replaced by Parvovirus B-19 (PVB-19) with a prevalence rate of 30%, followed by human herpes virus 6 (HHV-6) with a prevalence rate of 11% [73]. IM has been studied using murine models infected with CVB3, that resulted in the description of three infectious stages (acute, subacute and chronic). In the acute phase, lasting for about a few days, the virus infiltrates the myocytes. The second phase can take between several weeks up to a few months and is marked by the host's immune response, consisting in the activation of cytotoxic T cells, which determine the lysis of infected myocytes. The last phase has a similar duration as the subacute one, and is comprised of cardiac remodeling in the absence of myocytes that have been destroyed in the acute and subacute phase, and can lead to functionality improvement by inflammation resolving due to clearing out the virus, or in the worst case scenario it may lead to DCM. In general, patients who have acute viral myocarditis are asymptomatic, but one diagnosis clue that can be found in these patients are the frequent ventricular arrhythmias [77-81].

Myocarditis cases that come from Latin America are due to Chagas disease. An estimated number of 18-20 million people are infected by this protozoan each year. This

**Table 4. Etiological agents of IM** [69,73]

| Causative agents | Infectious myocarditis |
|---|---|
| Viruses | Coxsackie A and B<br>Echovirus<br>Poliovirus<br>Hepatitis A, B and C<br>Respiratory syncytial virus<br>Adenovirus<br>CMV<br>Parvo B19<br>Herpes simplex virus<br>HIV<br>Epstein-Barr virus<br>Yellow fever |
| Bacteria | *Corynebacterium diphtheriae*<br>*Streptococcus pneumoniae*<br>*Mycoplasma pneumoniae*<br>*Brucella* sp.<br>*Borrelia burgdorferi*<br>*Chlamydia psittaci*<br>*Coxiella burnetii**<br>*Rickettsia rickettsii*<br>*Neisseria meningitidis*<br>*Neisseria gonorrhoeae* |
| Protozoa | *Trypanosoma cruzi*<br>*Toxoplasma gondii* |
| Fungi | *Candida* sp.<br>*Cryptococcus* sp.<br>*Histoplasma* sp.<br>*Nocardia* sp.<br>*Aspergillus* sp. |
| Parasites | *Trichinella spiralis*<br>*Taenia solium*<br>*Echinococcus granulosus* |

***Note:*** **myocarditis is the most severe form of Q fever, being rarely documented* [74]

illness has a first asymptomatic - acute phase, and a second - chronic phase, consisting in cardiomyopathy and/or mega syndromes, which can be seen in 30% of the infected people [82 - 84].

Less frequently seen is bacterial myocarditis, often secondary to endocarditis, pneumonia, Rocky Mountain spotted fever, etc.

Myocarditis is the most common cause of death in diphtheria, but it also can lead to heart failure in 8-15% of the people infected with *Chlamydia psittaci*. IM can also occur in dengue fever, rheumatic fever, and in 1-8% of patients with Lyme disease [69, 73].

## INFECTIOUS PERICARDITIS

The pericardium functions as a barrier that limits the spread of infections and malignancies to the heart. Pericardial diseases can be classified in pericarditis (pericardium inflammation) or pericardial effusion, with infectious and noninfectious etiology (e.g. due to malignancy, uremia, and connective tissue disorders). Infectious pericarditis is related to hospital setting and endemic area. Pericarditis remains idiopathic in almost 80-85% of cases, while infective pericarditis has a rate of 6%. It can be acute (most frequent, <6 weeks), subacute (6 weeks - 6 months), recurrent (20-

**Table 5. Main etiological agents of infectious pericarditis**

| Type of infection | Acute pericarditis | Recurrent pericarditis |
|---|---|---|
| Viral | Echovirus<br>Parvovirus B19<br>HHV-6<br>Coxsackie virus<br>HIV<br>HBV<br>HCV<br>Rubella<br>Chickenpox<br>Paramyxovirus (mumps)<br>EBV<br>CMV<br>Influenza virus | Echovirus<br>Parvovirus B19<br>HHV-6<br>Coxsackie virus<br>Rubella<br>Chickenpox<br>Paramyxovirus (mumps)<br>Influenza virus<br>EBV<br>Adenovirus<br>HIV<br>HBV<br>HCV |
| Bacterial | Streptococci<br>*Staphylococcus* sp.<br>*Streptococcus pneumoniae*<br>*Norcardia* sp.<br>*Actinobacillus* sp.<br>*Rickettsia* sp.<br>*Neisseria meningitidis*<br>*Mycobacterium tuberculosis*<br>*Mycoplasma* sp.<br>*Haemophilus* sp.<br>*Chlamydia* sp.<br>*Legionella* sp.<br>*Listeria* sp.<br>*Coxiella burnetii* | *Coxiella burnetii*<br>*Streptococcus pneumoniae*<br>*Mycobacterium tuberculosis*<br>*Mycoplasma* sp.<br>*Haemophilus* sp.<br>*Staphylococcus* sp.<br>*Chlamydia* sp.<br>*Legionella* sp.<br>*Listeria* sp.<br>*Leptospira* sp.<br>*Neisseria gonorrhoeae*<br>*Neisseria meningitidis* |
| Fungal | *Histoplasma* sp.<br>*Candida* sp.<br>*Aspergillus* sp.<br>*Blastomyces* sp.<br>*Coccidioides* sp. | *Aspergillus* sp.<br>*Candida* sp.<br>*Histoplasma* sp.<br>*Blastomyces* sp. |
| Parasitic | *Echinococcus* sp.<br>*Toxoplasma* sp.<br>*Entamoeba* sp. | *Echinococcus* sp.<br>*Toxoplasma* sp. |

40% of time) or chronic (lasts longer than 3 months) [85-90].

Recurrent pericarditis is the most serious complication and needs to be distinguished from the continuous type. The European Society of Cardiology defines recurrent pericarditis as a new infectious episode that occurs after 4 to 6 weeks of complete resolution of symptoms with treatment; while continuous pericarditis makes reference to the recurrence of symptoms up to 6 weeks but no longer than 3 months and is due to inadequate treatment of the first episode of the disease. Infectious pericarditis can be benign (viral), purulent (bacterial) or granulomatous (*M. tuberculosis*, fungi). Table 5 presents the etiological agents for this pathology [86, 91-94].

In Western countries, the most common form of pericarditis is the acute one, with viral etiology, being hard to diagnose on account of its non-specificity (hardly set apart from the idiopathic form). Tuberculous pericarditis has a high incidence (70%) in Sub-Saharan Africa, rising over 90% when co-occurring with HIV infection and having a high mortality rate of almost 85%. Bacterial pericarditis is less noted

in Western countries, but if misdiagnosed it can be responsible for a 40% mortality rate. Brucellar pericarditis occurs in almost 1% of cases and is frequently secondary to endocarditis. Frequently, infections of the pericardium are caused by anaerobic bacteria (*B. fragilis* group, *Clostridium* sp., *Fusobacterium* sp., *Bifidobacterium* sp., *Peptostreptococcus* sp., *Actinomyces* sp.) [88, 89, 91, 95, 96].

There are five mechanisms that can lead to purulent pericarditis: through injuries following surgery and cardiothoracic trauma, hematogenous expansion (bacteremia related), expanding from a myocardial site (infections of myocardium and also endocardium), adjacent diffusion from an intrathoracic site and extending from a suppurative subdiaphragmatic location [89, 97].

Purulent pericarditis is typical for immunocompromised patients (HIV infected, undergoing dialysis, or chemotherapy, following thoracic trauma, etc.). The main etiological agents responsible for this type of pericarditis are Gram-positive bacteria and fungi, with a shift taking place in the recent years to Gram-negative bacteria. Frequent species identified in this pathology are *Staphylococcus aureus* (hematogenous spread, 22-31%), *Pneumococcus* sp. (adjacent diffusion from an intrathoracic site), *Borrelia burgdorferi*, *Coxiella burnetii* (5-7%), followed by infrequent pathogens such as *Haemophilus* sp., *Streptococcus* sp., *Chlamydia* sp., *Leptospira* sp., *Listeria* sp., *Providencia stuartii*. Fungal infections are thriving in immunocompromised patients, with species such as *Histoplasma sp.* (most frequent), *Aspergillus* sp., *Candida* sp. (especially *Candida albicans* and *C. tropicalis)* and *Blastomyces* sp. being detected [97 - 99].

Almost 20-30% cases of purulent pericarditis, with causative agents of bacterial nature, leads to constrictive pericarditis. Purulent pericarditis is derived in 70% of cases from infected areas adjacent to the pericardium, pneumonia being responsible for 25% of them. The mortality rate for this illness is between 30-50%, a main cause of this inflated rate being the high incidence (40%) of negative cultures [100, 101].

## INFECTIOUS COMPLICATIONS FOLLOWING HEART TRANSPLANT

As specified by the International Society for Heart and Lung Transplantation, between 1st July 2015 - 30th June 2016, 4,763 hearts were transplanted, of which 4,119 transplants were performed in adult and 642 in pediatric population. This surgical procedure is mostly used in non-ischemic cardiomyopathy, followed by ischemic cardiomyopathy and restrictive cardiomyopathy. Over the years, from 1992 to 2016, the sequence of these diseases for which heart transplant is necessary has not changed significantly [102]. Prior to the discovery of immunosuppressants, the cause of death was mainly organ rejection. Currently, the highest morbidity rate subsequent to heart transplantation is caused by graft rejection, followed by infection occurred in the first 30 days. Mortality caused by infections ranks first in the period of 30 days - 1 year post-transplantation, the incidence being of 65%, increasing to 85% after 5 years and reaching a peak of 91% after 10 years [103, 104].

Depending on their emergence, post-transplant infections can be classified as: i) early infections - <1 month post-transplant (Vancomycin-resistant enterococci, MRSA, *Clostridium difficile*, *Pseudomonas* sp., *Nocardia* sp., Herpes simplex virus, *Candida* sp., *Aspergillus* sp.); ii) intermediate infections - 1-6 months post-transplant (*Nocardia* sp., *Clostridium difficile*, *Mycobacterium tuberculosis*, *Listeria monocytogenes*, Cytomegalovirus (CMV), HHV-6, Adenovirus, Influenza virus, Hepatitis C, Hepatitis B, Epstein-Barr virus (EBV), *Candida* sp., *Aspergillus* sp., *Pneumocystis carinii*, *Cryptococcus* sp., *Toxoplasma gondii*); iii) late infections - >6 months post-transplant (*Nocardia* sp., *Mycobacterium tuberculosis*, *Listeria monocytogenes*, Herpes simplex virus, Varicella Zoster virus, CMV, Hepatitis C, Hepatitis B, *Aspergillus* sp., *Pneumocystis carinii*, *Cryptococcus* sp., *Toxoplasma gondii*, *Trypanosoma cruzi*) [104-107].

Due to immunosuppressants, sudden and long-term post-transplant infections are a common complication. The immunosuppressants increase the emergence of opportunistic pathogens (CMV, EBV, *Pneumocystis jiroveci*,

**Table 6. Preoperative testing for donors and recipients that will undergo heart transplant**
*(adapted after Hummel, 2011)*

| Type of examination | Donor | Recipient |
|---|---|---|
| Serology | **HIV**<br>**EBV**<br>**HCV**, **HBV** (15%, respectively 16.3% post-transplant incidence in the 90's; according to a study in Italy, HBV has a 5% reactivation rate) [110, 111]<br>**CMV** (a 9-35% rate in the first 6 months post-transplant; when infected with this virus, the rate of opportunistic infections rises and several studies suggest that the virus can be highly correlated with cardiac allograft vasculopathy) [112 - 115]<br>**toxoplasmosis** (two studies indicate that the serological status of patients does not influence mortality) [116, 117] | |
| | Venereal Disease Research Laboratory test (VDRL) | Syphilis |
| Culture | Organ perfusate<br>Transport media | Smears for MRSA diagnosis<br>Stool specimens for *C. difficile* diagnosis |
| Other diagnosis | Blood culture | CT, X-ray |

etc.). Also, environmental factors may increase the likelihood of infections through airborne fungal spores (*Aspergillus* sp.; *Blastomyces* sp.; *Cryptococcus* sp.; *Candida* sp.), water contamination with *Legionella* sp., and visitors who may be carriers of various viruses and bacteria. A greater threat poses the hospital staff, because they can easily spread infections from one patient to another if they do not follow prevention of hospital-acquired infections protocol (*Clostridium difficile* infection has 4% incidence, bacterial pneumonia - 25%, bacteremia - 15%) [108-109].

In order to avoid the risk of infection increasing among transplant patients, the donor and recipient will be submitted to preoperative testing shown in Table 6.

Although there is a low incidence of fungal infections, these pathogens remain the main cause of post-transplant mortality (30-100%). The most frequently involved fungi are *Candida* sp. and *Aspergillus* sp., especially *A. fumigatus*, presenting a higher risk of mortality because it causes pulmonary aspergillosis in the first 3 months post-transplant (almost 24-40 days, with an incidence of 70%). Infection with *Candida* sp. occurs after 45 days and has gastrointestinal origin. Although these species are more frequently identified in clinic than *Aspergillus* sp., they are rarely invasive, generally localizing at the skin and mucous membranes level [118 - 120].

## VENTRICULAR ASSIST DEVICES (VAD) ASSOCIATED INFECTIONS

Despite of the fact that heart transplant is the ideal treatment for heart failure, the number of available hearts from donors falls short when compared to the number of recipients. To prolong patients' life until cardiac transplantation, the recipient can use ventricular assist devices (VADs) for a long period of time.

Although these devices can be inserted for an indefinite period of time, those who wear them have a high risk of infection, estimated at 14% - 50% during the period of VAD use [121]. According to the International Society for Heart and Lung Transplantation, there are 3 types of infections in pre-transplant patients with VAD: i) VAD-specific infections, when pathogens infect the device (cannula sing, pump, percutaneous driveline, pocket infections); ii) VAD-related infections, occurring as well in patients that do not have the device (bloodstream infections, endocarditis); iii) non-VAD infections, unrelated to the devices (urinary tract infections, lower respiratory tract infections, *Clostridium difficile* infections) [122].

**Table 7. Pathogens involved in VAD infections regardless of the source of contamination** [121, 122, 126, 127]

| Period of data collection | 1995-2016 |
|---|---|
| Number of cases | 132 |
| CoNS | 36 (27.27%) |
| Methicillin-resistant *S. aureus* (MRSA) | 28 (21.21%) |
| Vancomycin-susceptible enterococci (VSE) | 20 (15.15%) |
| *Enterobacter* sp. | 20 (15.15%) |
| Vancomycin-resistant enterococci (VRE) | 16 (12.12%) |
| Methicillin-susceptible *S. aureus* (MSSA) | 15 (11.36%) |
| *Escherichia coli* | 15 (11.36%) |
| *Serratia* sp. | 12 (9.09%) |
| *Proteus* sp. | 11 (8.33%) |
| *Pseudomonas aeruginosa* | 11 (8.33%) |
| *Candida albicans* | 5 (3.79%) |
| Other | 42 (31.82%) |

Etiological agents are identical, regardless of the site where the infection is identified, i.e.: CoNS, *Staphylococcus aureus*, *Enterococcus* sp., Gram-negative bacilli (Table 7) [121, 123]. Percutaneous driveline infections have the highest incidence, followed by pocket infections. Pathogens related to percutaneous driveline infections belong to the skin microbiota, being

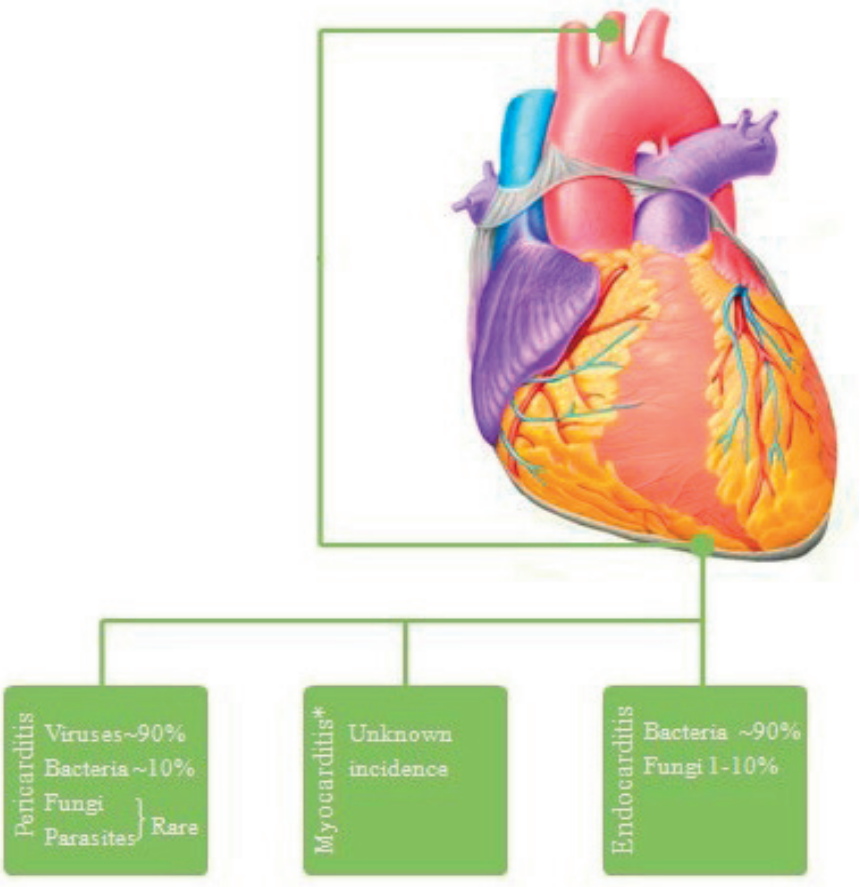


**Fig. 3. Etiology of heart infections taking into consideration the three layers of the heart (*Note: *the incidence rate of infectious myocarditis is still unknown)***

isolated in a higher number than those related to pocket contamination. Thereby, in the first case, infection can be polymicrobial and can include multi-resistant pathogens, while when affecting the pockets a single microorganism is identified [124, 125].

Taken together, the available data regarding the etiology of heart infections with different localizations are synthesized in Fig. 3 [32-41, 93, 98].

## CONCLUSIONS

With the increasing prevalence of CVDs, the risk of infection is also on the rise, due to the aging of the population, associated with a growing rate of cardiac surgery and use of cardiac devices, the presence of various pathologies such as HIV infection, diabetes, renal failure, autoimmune disease, and CHD. Different viral, bacterial, fungal and protozoa pathogens can specifically infect all heart layers, from endocardium to myocardium and pericardium, the etiology depending on the geographical area, the immune status of the patient and comorbidities (Fig. 3).

The proper management of heart infections requires the technical capability of early laboratory diagnosis, guidelines for the hospital-acquired infections control and epidemiological studies to establish the incidence of different infectious agents in a certain geographical area.

**Conflict of interests:** None to declare.

**Acknowledgements**

The authors gratefully acknowledge the financial support of Research project PN-111-P4-ID-**PCCF**-2016-0114.

## REFERENCES

1. Allam AH, Thompson RC, Wann LS, Miyamoto MI, Thomas GS. Computed Tomographic Assessment of Atherosclerosis in Ancient Egyptian Mummies. JAMA. 2094-2091:(19)302;2009.
2. A history of cardiovascular disease epidemiology (2012, October). Retrieved December 15, 2017, from http://www.epi.umn.edu/cvdepi/history-overview.
3. A brief history of heart transplantation (no date). Retrieved December 15, 2017, from http://columbiasurgery.org/heart-transplant/brief-history-heart-transplantation.
4. Strong A, Musunuru K et al. Genome editing in cardiovascular diseases. Nat Rev Cardiol. 2017;14(1):11-20.
5. Randles A, Frakes DH, and Leopold JA. Computational fluid dynamics and additive manufacturing to diagnose and treat cardiovascular disease. Trends in Biotechnology. 2017;35(11):1049-1061.
6. W. Jiang et al. Nanomaterials for treating cardiovascular diseases: A review. Bioactive Materials. 2017;2(4):185-198.
7. Behairy OG et al. Influence of early feeding practices on biomarkers of cardiovascular disease risk in later life. Egyptian Pediatric Association Gazette. 2017;65(4):114-121.
8. Naghavi, Mohsen et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017;390(10100):1151-1210.
9. Boeder NF, et al. Endocarditis after interventional repair of themitral valve: Review of a dilemma. Cardiovascular Revascularization Medicine. 2016;18(2):141-144.
10. Sandoe JAT, et al. Infective endocarditis in the adult patient. Medicine. 2017;45(11):678-682.
11. Sistino JJ and Fitzgerald DC. Epidemiology of cardiovascular disease in the United States: implications for the perfusion profession. A 2017 update. Perfusion. 2017;32(6):501-506.
12. Dayer M et al. Is antibiotic prophylaxis to prevent infective endocarditis worthwhile? Journal of Infection and Chemotherapy. 2017;24(1):18-24.
13. Pavel Gregor. What's new in the prevention of infective endocarditis? Cor et Vasa. 2013;55(6):520–524.
14. McIntyre V et al. Recurrent infective endocarditis causing heart valve failure: A case report. Human Pathology: Case Reports. 2017;10:39–42.
15. Delahaye F, Duclos A. Is Infective Endocarditis Changing Over Time? Journal of the American College of Cardiology. 2017;70(22):2805-2807.
16. Harsh Barot, Fahad Alsindi. Endocarditis, Hospital Medicine Clinics. 2017;6(2):229–243.
17. Juttukonda, Lillian J. et al. Dietary Manganese Promotes Staphylococcal Infection of the Heart. Cell Host & Microbe. 2017;22(4):531-542.

18. Dugdale, Caitlin et al. Out of Sight: Culture-Negative Endocarditis and Endophthalmitis. The American Journal of Medicine. 2017;130(2):51-53.
19. C.A. Timmer et al.. Recurrent infective endocarditis as a manifestation of Loeffler's endocarditis: The diagnostic importance of cardiac magnetic resonance imaging. Cor et Vasa. 2017;530:1-4.
20. George E. Burch, Nicholas P. DePasquale. Viral endocarditis. American Heart Journal. 1964;67(6):721-723.
21. Fournier PE, Charrel R, Raoult D. Viral Endocarditis or Simple Viral Disseminated Infection? Clinical Infectious Diseases. 2011;53(12):1298.
22. Stear TJ, Shersher D, Kim GJ, Smego DR. Valvular Cytomegalovirus Endocarditis. Ann Thorac Surg. 2016;102(2):105–107.
23. Pasha, Ahmed & Lee, Justin & Low, See Wei & Desai, Hem & Lee, Kwan & Al Mohajer, Mayar. Fungal Endocarditis-Update on Diagnosis and Management. The American Journal of Medicine. 2016;129(10):1037-1043.
24. Shi-Min Yuan. Fungal Endocarditis. Braz J Cardiovasc Surg. 2016;31(3):252-255.
25. Chinen K. et al. Fungal infections of the heart: A clinicopathologic study of 50 autopsy cases. Pathology – Research and Practice. 2007;203(10):705-715.
26. Bandyopadhyay S, Tiwary PK, Mondal S, Puthran S. Pacemaker lead Candida endocarditis: Is medical treatment possible? Indian Heart Journal. 2015;67(3):100-102.
27. Negi, N., Ahmad, A. Current updates on fungal endocarditis. Fungal Biology Reviews. 2018;32(1):1-9.
28. Badiee P, Amirghofran AA, Nour MG, Shafa M, Nemati MH. Incidence and Outcome of Documented Fungal Endocarditis. Int Cardiovasc Res J. 2014;8(4):152-155.
29. Badiee P, Amirghofran AA, Nour MG. Evaluation of noninvasive methods for the diagnosis of fungal endocarditis. Medical Mycology. 2014;52(5):528-534;
30. Fujii S, Tugaleva E, Chu MWA, Bainbridge D. A Curious Case of Blood Culture Negative Infective Endocarditis. Journal of Cardiothoracic and Vascular Anesthesia. 2018;32(1):3-5.
31. El-Chakhtoura, Nadim et al. A 27-year experience with infective endocarditis in Lebanon. Journal of Infection and Public Health. 2017;10(6):734-739.
32. Kiyoyuki Eishi, et al. Surgical management of infective endocarditis associated with cerebral complications. Multi-center retrospective study in Japan. J Thorac Cardiovasc Surg. 1995;110(6):1745-1755.
33. Nakagawa T, Wada H, Sakakura K, Yamada Y, Ishida K, Ibe T, et al. Clinical features of infective endocarditis: comparison between the 1990s and 2000s. Journal of Cardiology. 2014;63(2):145-148.
34. Netzer RO, Zollinger E, Seiler C, Cerny A. Infective endocarditis: clinical spectrum, presentation and outcome. An analysis of 212 cases 1980-1995. Heart. 2000;84(1):25-30.
35. Fefer P, Raveh D, Rudensky B, Schlesinger Y, Yinnon AM. Changing epidemiology of infective endocarditis: A retrospective survey of 108 cases, 1990-1999. European Journal of Clinical Microbiology and Infectious Diseases. 2002;21(6):432-437.
36. Yoshinaga M, Niwa K, Niwa A, Naruhiko I, Hideto T, Shigeyuki E, et al. Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. The American Journal of Cardiology. 2008;101(1):114-118.
37. Bínová J, Kubánek M, Koudelková E, Vrbská J, Kettner J, Kačer P, et al. Changing profile of infective endocarditis in patients hospitalised in a tertiary Czech hospital from 2000 to 2013. Cor et Vasa. 2016;58(6):576-583.
38. Olmos C, Vilacosta I, Fernández-Pérez C, Bernal JL, Ferrera C, García-Arribas D, et al. The evolving nature of infective endocarditis in Spain: A population - based study (2003 to 2014). Journal of the American College of Cardiology. 2017;70(22):2795-2804.
39. Elbey MA, Akdağ S, Kalkan ME, Kaya MG, Sayın MR, Karapınar H, et al. A multicenter study on experience of 13 tertiary hospitals in Turkey in patients with infective endocarditis. Anadolu Kardiyol Derg. 2013;13(6):523-527.
40. Bassetti M, Venturini S, Crapis M, Ansaldi F, Orsi A, Della Mattia A, et al. "Friuli Venezia Giulia Endocarditis study group" Rita Piazza, Grazia Fazio, Vito Di Piazza, Mario Maschio, Anna Beltrame. Infective endocarditis in eldery: An Italian prospective multi-center observational study. International Journal of Cardiology. 2014;177(2):636-638.
41. Slipczuk L, Codolosa JN, Davila CD, Romero-Corral A, Yun J, et al. Infective Endocarditis Epidemiology Over Five Decades: A Systematic Review. PLOS ONE. 2014;9(10):e111564.
42. Smulyan H, Blair DC. The Tale of Infective

Endocarditis: Fatal Then Curable but Rarely Preventable. Am J Med Sci. 2015;350(2):140–146.
43. Letaief A, Boughzala E, Kaabia N, Ernez S, Abid F, Chaabane TB, et al. Epidemiology of infective endocarditis in Tunisia: a 10-year multicenter retrospective study. International Journal of Infectious Diseases. 2007;11(5):430-433.
44. Durante-Mangoni E, Bradley S, Selton-Suty C, Tripodi MF, Barsic B, Bouza E, et al. Current Features of Infective Endocarditis in Elderly Patients. Arch Intern Med. 2008;168(19):2095-2103.
45. Mylotte D, Rushani D, Therrien J, Guo L, Liu A, Guo K, Incidence, Predictors and Mortality of Infective Endocarditis in Adults with Congenital Heart Disease Without Prosthetic Valves. The American Journal of Cardiology. 2017;120(12):2278-2283.
46. Bauer UMM, et al. Are adults with congenital heart disease informed about their risk for infective endocarditis and treated in accordance to current guidelines?. Int J Cardiol. 2017;245:105-108.
47. Vogkou CT, Vlachogiannis NI, Palaiodimos L,. Kousoulis AA. The causative agents in infective endocarditis: a systematic review comprising 33,214 cases. European Journal of Clinical Microbiology and Infectious Diseases. 2016;35(8):1227-1245.
48. R. Carapetis. Rheumatic Heart Disease in Asia. Circulation. 2008;118(25):2748-2753.
49. David A. Watkins, et al.. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990–2015. The New England Journal of Medicine. 2017;377(8):713-722.
50. van der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, et al. Birth Prevalence of Congenital Heart Disease Worldwide A Systematic Review and Meta-Analysis. Journal of the American College of Cardiology. 2011;58(21):2241-2247.
51. Kestler M, Muñoz P, Marín M, Goenaga MA, Idígoras Viedma P, de Alarcón A, et al. Hidalgo-Tenorio C, Moreno M, Bouza E, on behalf of the Spanish Collaboration on Endocarditis (GAMES). Endocarditis caused by anaerobic bacteria. Anaerobe. 2017;47:33-38.
52. Faure E, et al. Haemophilus parainfluenzae endocarditis in young adults. Médecine et Maladies Infectieuses. 2017;47(1):58-60.
53. Garcıa-Granja et al. Polymicrobial Infective Endocarditis: Clinical Features and Prognosis. Medicine. 2015;94(49):e2000.
54. Imai A, Gotoh K, Asano Y, Yamada N, Motooka D, Fukushima M, et al. Comprehensive metagenomic approach for detecting causative microorganisms in culture-negative infective endocarditis. International Journal of Cardiology. 2014;172(2):288-289.
55. Oprea M, Surdeanu M, Badescu D, Cotar AI, Dinu S, Banu O, et al. Contributions of ENDOBACT multicentric study to the infective endocarditis etiology in Romania. Revista Română de Medicină de Laborator. 2013;21(2/4):197-208.
56. Subedi, S. et al. Laboratory Approach to the Diagnosis of Culture-Negative Infective Endocarditis. Heart, Lung and Circulation. 2017;26(8):763-771.
57. Gnanenthiran SR et al. Prosthetic Valve Infective Endocarditis With Mycobacterium Fortuitum: Antibiotics Alone Can Be Curative. Heart, Lung and Circulation. 2017;26(11):86-89.
58. Cotar AI, Badescu D, Oprea M, Dinu S, Banu O, Dobreanu D, et al. Q Fever Endocarditis in Romania: The First Cases Confirmed by Direct Sequencing. Int J Mol Sci.9513-9504:(12)12;2011.
59. Fenollar F, Fournier PE, Raoult D. Molecular Detection of Coxiella burnetii in the Sera of Patients with Q Fever Endocarditis or Vascular Infection. Journal of Clinical Microbiology. 2004;42(11):4919-4924.
60. Bozkurt I, Coksevim M, Cerik IB, Gulel O, Tanyel E, Leblebicioglu H. Infective endocarditis with atypical clinical feature and relapse by Abiotrophia defectiva. J Saudi Heart Assoc. 2017;29(2):136–138.
61. Murillo H, et al. Infectious Diseases of the Heart: Pathophysiology, Clinical and Imaging Overview. RadioGraphics. 2016;36(4):963–983.
62. Hussain ST, Witten J, Shrestha NK, Blackstone EH, Pettersson GB. Tricuspid valve endocarditis. Ann Cardiothorac Surg. 2017;6(3):255-261.
63. Shi-Min Yuan. Right-sided infective endocarditis: recent epidemiologic changes. Int J Clin Exp Med. 2014;7(1):199-218.
64. Dyson C, Barnes RA, Harrison GAJ. Infective endocarditis: an epidemiological review of 128 episodes. Journal of Infection. 1999;38(2):87-93.
65. Werdan K et al. Mechanisms of infective endocarditis: pathogen–host interaction and risk states. Nat Rev Cardiol. 2014;11(1):35-50.
66. Vallejo FAG. Epidemiology of Infective Endocarditis (2016, November 9). Retrieved January 5, 2018, from https://www.intechopen.com/books/contemporary-challenges-in-endocarditis/epidemiology-of-infective-endocarditis

67. Yang F, et al. Epidemiology and the prognosis of healthcare-associated infective endocarditis in China: the significance of non-nosocomial acquisition. Emerging Microbes and Infections. 2015;4(7):e38.
68. 68. Holland TL, Baddour LM,. Bayer AS, Hoen B, Miro JM, Fowler Jr. VG. Infective endocarditis. Nat Rev Dis Primers. 2017;2:e16059.
69. 69. Friman G, Wesslen L, Fohlman J, Karjalainenj J, Rolf C. The epidemiology of infectious myocarditis, lymphocytic myocarditis and dilated cardiomyopathy. European Heart Journal. 1995;16:36-41.
70. Jensen LD, Marchant DJ. Emerging Pharmacologic, Targets and Treatments for Myocarditis. Pharmacology and Therapeutics. 2016;161:40-51.
71. Krejci J, Mlejnek D, Sochorova D, Nemec P. Inflammatory Cardiomyopathy: A Current View on the Pathophysiology, Diagnosis, and Treatment. BioMed Research International. 2016;2016:e4087632.
72. Massilamany C, Huber SA, Cunningham MW, Reddy J. Relevance of Molecular Mimicry in the Mediation of Infectious Myocarditis. J Cardiovasc Transl Res. 2014;7(2): 165–171.
73. Ginsberg, F et al. Fulminant Myocarditis. Critical Care Clinics. 2013;29(3):465-483.
74. Miguel F. Carrascosa, Francisco Pascual Velasco, Rubén Gómez Izquierdo, José R. Salcines-Caviedes, Verónica Gómez Amigo, Ana M. Canga-Villegas. Acute Q fever myocarditis: Thinking about a life-threatening but potentially curable condition. International Journal of Cardiology. 2012;158(1):17-19.
75. Engler RJM, Nelson MR, Collins Jr. LC, Spooner C, Hemann BA, et al. A Prospective Study of the Incidence of Myocarditis/Pericarditis and New Onset Cardiac Symptoms following Smallpox and Influenza Vaccination. PLOS ONE. 2015;10(3):e0118283.
76. Noel R. Rose. Viral Myocarditis. Curr Opin Rheumatol. 2016;28(4):383–389.
77. Massilamany C, Gangaplara A, Reddy J. Intricacies of cardiac damage in coxsackievirus B3 infection: Implications for therapy. Int J Cardiol. 2014;177(2):330–339.
78. Yajima T. Viral myocarditis: potential defense mechanisms within the cardiomyocyte against virus infection. Future Microbiol. 2011;6(5):551–566.
79. Robert Dennert, Harry J. Crijns, Stephane Heymans. Acute viral myocarditis. European Heart Journal. 2008;29(17):2073–2082.
80. Kindermann I, Barth C, Mahfoud F, Ukena C, Lenski M, Yilmaz A, Klingel K, Reinhard Kandolf, Udo Sechtem, Leslie T. Cooper, Michael Böhm. Update on Myocarditis. Journal of the American College of Cardiology. 2012;59(9):779–792.
81. Baksi AJ, Kanaganayagam GS, Prasad SK. Arrhythmias in Viral Myocarditis and Pericarditis. Card Electrophysiol Clin. 2015;7(2):269-281.
82. Lewis MD, Kelly JM, et al. Putting Infection Dynamics at the Heart of Chagas Disease. Trends in Parasitology. 2016;32(11):899-911.
83. Roffê E, Rothfuchs AG, Santiago HC, Marino APMP, Ribeiro-Gomes FL, Eckhaus M, et al.. IL-10 Limits Parasite Burden and Protects against Fatal Myocarditis in a Mouse Model of Trypanosoma cruzi Infection. Immunol. 2012;188(2):649–660.
84. Nagajyothi F, Weiss LM, Zhao D, Koba W, Jelicks LA, et al. High Fat Diet Modulates Trypanosoma cruzi Infection Associated Myocarditis. PLOS Neglected Tropical Diseases. 2014;8(10):e3118.
85. Khandaker MH, Espinosa RE, Nishimura RA, Sinak LJ, Hayes SN, Melduni RM, et al. Pericardial Disease: Diagnosis and Management, Mayo Clin Proc. 2010;85(6):572-593.
86. 86. Doctor NS, Shah AB, Coplan N, Kronzon I. Acute Pericarditis. Progress in Cardiovascular Diseases. 2017;59(4):349-359.
87. 87. Zumla A, Maeurer M, Moll G, Mayosi BM. Host-directed therapies for tuberculous pericarditis. International Journal of Infectious Diseases. 2015;32:30–31.
88. Sheth S, Wang DD, Kasapis C. Current and emerging strategies for the treatment of acute pericarditis: a systematic review. Journal of Inflammation Research. 2010;3:135-142.
89. Brook I. Pericarditis caused by anaerobic bacteria. International Journal of Antimicrobial Agents. 2009;33(4);297-300.
90. Imazio M, Gribaudo E, Gaita F. Recurrent Pericarditis. Progress in Cardiovascular Diseases. 2017;59(4):360-368.
91. Imazio M, Trinchero R. Triage and management of acute pericarditis, International Journal of Cardiology. 2007;118(3):286-294.
92. Foerg F, Gardner Z. Pericarditis. Hospital Medicine Clinics. 2015;4(2):205-215.
93. Brucato A, Maestroni S, Cumetti D, Thiella G, Alari G, Brambilla G, Imazio M, Doria A, Palmieri G, Adler Y. Recurrent pericarditis:

Infectious or autoimmune? Autoimmunity Reviews. 2008;8(1):44-47.
94. Imazio M, Gaita F. Acute and Recurrent Pericarditis. Cardiol Clin. 2017;35(4):505-513
95. Kloos JA. Characteristics, Complications, and Treatment of Acute Pericarditis. Crit Care Nurs Clin North Am. 2015;27(4):483-497.
96. Kaya S, Eskazan AE, Elaldi N. Brucellar pericarditis: a report of four cases and review of the literature. International Journal of Infectious Diseases. 2013;17(6):428-432.
97. Ferreira dos Santos L, Moreira D, Ribeiro P, et al. Pericardite purulenta: um diagnóstico raro. Rev Port Cardiol. 2013;32(9):721-727.
98. Shiber JR. Purulent Pericarditis: Acute Infections and Chronic Complications. Hospital Physician. 2008;45:9-17.
99. Chang S-A. Tuberculous and Infectious Pericarditis. Cardiology Clinics. 2017;35(4):615-622.
100. Lizano MTR, Iglesias PP, Koller T, Serrano JG, Hittinger MLM, Huerta BM. Pericardial disease after cardiac surgery: postpericardiotomy syndrome, purulent and constrictive pericarditis. Journal of Cardiothoracic and Vascular Anesthesia. 2017;31(1):28-29.
101. Wright NR, Pfahl KW, Bush CA. Purulent Pericarditis and Abscessed Myocardium with Acute Myocardial Infarction. The American Journal of Medicine. 2016;129(5):15-16.
102. Introduction/General statistics (2017, October). Retrieved February 8, 2018, from http://www.ishlt.org/registries.
103. Kirklin JK, Naftel DC, Bourge RC, McGiffin DC, Hill JA, Rodeheffer RJ, et al. Evolving trends in risk profiles and causes of death after heart transplantation: A ten-year multi-institutional study. J P. J. Thorac Cardiovasc Surg. 2003;125(4):881-890.
104. Alba C, Bain E, Ng N, Stein M, Brien KO, et al. Complications after Heart Transplantation: Hope for the Best, but Prepare for the Worst. Int J Transplant Res Med. 2016;2(2):022.
105. Linder J. Infection as a complication of heart transplantation. J Heart Transplant. 1988;7(5):390-394.
106. Montoya JG, Giraldo LF, Bradley E, Stinson EB, Gamberg Pt, Hunt S, et al. Infectious Complications among 620 Consecutive Heart Transplant Patients at Stanford University Medical Center. Clinical Infectious Diseases. 2001;33(5):629-640.
107. Joung MK, Kang CI, Lee JA, Moon S, Chung DR, Song JH, et al. Clinical features and outcome of infectious complications in heart transplant recipients in Korea. Infect Chemother. 2010;42(6):375-382.
108. Hummel M, Early postoperative therapy after heart transplantation: Prophylaxis, diagnosis and antibiotic, antimycotic and antiviral therapy of infections. Applied Cardiopulmonary Pathophysiology. 2011;15:245-255.
109. Clauss, Heather E.Suh, Byungse, et al. Infections in Heart and Lung Transplant Recipients. Clinical Microbiology Newsletter. 2012;34(3):19-25.
110. Vitronea M, Iossaa D, Rinaldia L, Pafundia PC, Molaroa R, Parrellaa A, et al. Hepatitis B virus reactivation after heart transplant: Incidence and clinical impact. Journal of Clinical Virology. 2017;96:54–59.
111. Lunel F, et al. Hepatitis Virus Infections in Heart Transplant Recipients: Epidemiology, Natural History, Characteristics, and Impact on Survival. Gastroenterology. 2000;119(4):1064-1074.
112. Durante-Mangoni E, Andini R, Pinto D, Iossa D, Molaro R, Agrusta F, Casillo R, Grimaldi M, Utili R. Effect of the immunosuppressive regimen on the incidence of cytomegalovirus infection in 378 heart transplant recipients: A single centre, prospective cohort study. Journal of Clinical Virology. 2015;68:37–42.
113. Ţilea B, Șincu N, Teches S, Ispas M, Ţilea I. Infectious complications in heart transplant patients. BMC Infectious Diseases. 2014;14(7):O18.
114. Delgado JF, Reyne AG, deDios S, López-Medrano F, Jurado A, SanJuan R, et al. Influence of cytomegalovirus infection in the development of cardiac allograft vasculopathy after heart transplantation. J Heart Lung Transplant. 2015;34(8):1112–1119.
115. Haddad F, Deuse T, Pham M, Khazanie P, Rosso F, Luikart H, et al. Changing trends in infectious disease in heart transplantation. J Heart Lung Transplant. 2010;29:306–15.
116. Barge-Caballero E, et al., Preoperative Toxoplasma gondii serostatus does not affect long-term survival of cardiac transplant recipients. Analysis of the Spanish Heart Transplantation Registry. Int J Cardiol. 2018;250:183-187.
117. Chehrazi-Raffle A, Luu M, Yu Z, Liou F., Kittleson M., Hamilton M., et al.. Toxoplasma gondii Serology and Outcomes After Heart Transplantation: Contention in the Literature.

Transplantation Proceedings. 2015;47(6):1949-53.
118. Gurguí M, Muñoz P. Infecciones en el trasplante cardíaco. Enferm Infecc Microbiol Clin. 2007;25(9):587-98.
119. McCartney SL, Patel C, Del Rio JM. Long-term outcomes and management of the heart transplant recipient. Best Pract Res Clin Anaesthesiol. 248-237:(2)31;2017.
120. Neofytos D, Fishman JA, Horn D, Anaissie E, Chang C-H, Olyaei A, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis. 2010;12(3)220-229.
121. Monkowski DH, Axelrod P, Fekete T, Hollander T, Furukawa S, Samuel R. Infections associated with ventricular assist devices: epidemiology and effect on prognosis after transplantation. Transpl Infect Dis. 2007;9(2):114-120.
122. Héquet D, Kralidis G, Carrel T, et al. Ventricular assist devices as bridge to heart transplantation: impact on post-transplant infections. BMC Infectious Diseases. 2016;16:321;
123. Chambers HE, Pelish P, Qiu F, Florescu DF. Perioperative Prophylaxis for Total Artificial Heart Transplantation. Transplantation Proceedings. 2017;49(9):2169-2175.
124. Leuck AM. Left ventricular assist device driveline infections: recent advances and future goals. J Thorac Dis. 2015;7(12):2151-2157.
125. Califano S, Pagani FD, Malani Preeti N. Left Ventricular Assist Device–Associated Infections. Infect Dis Clin North Am. 2012;26(1):77–87.
126. Papathanasiou M et al. Colonization With Multiresistant Bacteria: Impact on Ventricular Assist Device Patients. The Annals of Thoracic Surgery. 2018;105(2):557-563.
127. Ryuichiro A et al. Factors Related to the Severity of Early Postoperative Infection After Heart Transplantation in Patients Surviving Prolonged Mechanical Support Periods: Experience at a Single University. Journal of Cardiothoracic and Vascular Anesthesia. 2018;32(1):53-59.