Chapter

Infective Endocarditis: Inflammatory Response, Genetic Susceptibility, Oxidative Stress, and Multiple Organ Failure

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Abstract

Infective endocarditis is defined by a focus of infection within the heart. Despite the optimal care, the mortality approaches 30% at 1 year, so the care for this type of patients represents a challenge to improve the result in your care. The challenges in this clinical entity have several aspects such as the diversity of germs that cause endocarditis, and the most important epidemiologically has generated resistance to antimicrobial treatment along with the possibility of apoptosis in their host-germ interaction. The immunogenetic susceptibility to host infection is discussed, which represents a deep area of research. Inflammation, local and systemic, is complex, with the genesis of reactive oxygen species, which are harmful when the antioxidant defenses are exceeded, causing the break in the mitochondrial electron transport chain with the fall in energy genesis, multiple organ failure, and death. Both at the cellular level and in the mitochondria, possible therapeutic targets are also commented.

Keywords: infective endocarditis, *Staphylococcus aureus*, single nucleotide polymorphism (SNP), inflammatory response, reactive oxygen species (ROS), oxidative stress, multiple organ failure (MOF)

1. Introduction

In this chapter we will analyze the physiopathological changes involved in the inflammatory response of the septic process in infective endocarditis [IE] that culminate with cellular damage and the generation of organic failures; morphological changes, cellular biology, biochemistry, immunology, and genetic vulnerability, which together are called "pathobiology," are the substrate of clinical manifestations of this serious disease, which requires a multidisciplinary group of experts

(cardiologists, infectologists, surgeons, intensivists) to optimize therapeutic approach. IE is defined as a severe multisystem disease, which results from an infection, often bacterial, that initially affects the endocardial surface of the heart [1]. The epidemiological pattern has changed over time [2–4]. The incidence has increased in recent years to 5–10 cases per 100,000 inhabitants [2], due to the fact of a greater number of predisposing factors such as the use of permanent cardiovascular devices, invasion with intravenous catheters in critical care units, and hemodialysis treatments, in addition to having greater accessibility to diagnostic tools. From the etiological point of view, *Staphylococcus aureus* (*S. aureus*) is predominant as a causal germ [5, 6]. The clinical course of a patient with IE depends on the inflammatory response, since it is variable; it also depends on the germ and the response of the patient to infection with varying degrees of hemodynamic and metabolic compromise [7–9]. We emphasize the current trend of the search for organic failures associated to the septic processes for their identification and stratification and therapeutic approach [10]. Given the characteristics of the disease, IE has a high mortality that goes from 20 to 30% in the reported series [2, 11]; it is noteworthy that the evolution toward septic shock has been documented in 30% [12], considering this complication as an independent variable of poor prognosis [13].

2. Epidemiology of infective endocarditis

The pathogenesis and the prognosis of IE can be simply described in a general way as the interaction between the host and the germ; however, these factors are not independent and are very importantly linked both in the susceptibility characteristics of the host (advanced age, higher prevalence of comorbid conditions, and exposure to health care) to survive or not to an infectious state, as of the characteristics of the germ involved. To reduce the incidence of IE and improve its outcome, epidemiological studies can provide valuable information on contemporary and modifiable risks to modify their morbidity and mortality [14].

The incidence of hospital discharge diagnoses for drug dependence combined with IE increased more than twelvefold from 0.2 to 2.7 per 100,000 persons per year over this 6-year period. Correspondingly, hospital costs for these patients increased eighteenfold, from $1.1 million in 2010 to $22.2 million in 2015 [15].

In another study also conducted in the USA, using a national sample of hospitalized patients from 1998 to 2009 with focus on IE showed an increase in the use of intracardiac devices from 13.3 to 18.9%. In cases with pathogens identified, *S. aureus* was the most common, increasing from 37.6% in 1998 to 49.3% in 2009, 53.3% of which were methicillin-resistant *Staphylococcus aureus* (MRSA) [16]. The above can give us an idea of the economic and assistance impact of treating patients with severe sepsis such as IE. It is an infection inside the organ that is responsible for distributing blood to practically the whole organism.

The evolution of an inflammatory process plus infection frequently occurs with clinical manifestations unspecified such as fever or hypothermia, tachycardia, tachypnea, or abnormal white blood cell count, progressing to septic shock and acute organ failure [17].

Epidemiological data of more than five decades tell us that *S. aureus* is the most important causal agent of IE [4]; so in the development of systemic inflammation that is generated by the host-germ interaction, we will consider the *S. aureus* as the best example of IE due to its virulence and an emergent property that we know as resistance to antibiotics, sophisticated defense mechanisms, and the ability to cause apoptosis in cells when it is alive inside the cell. The interaction of *S. aureus*-host allows us to develop in a substantive way, on one hand, the importance of the

virulence of the germ and, on the other, the defense mechanisms of the host, showing how the inflammation is generated and amplified to offer a step to oxidative stress. It is important to mention that other agents can cause IE such as streptococci and fungi.

3. *Staphylococcus aureus*

S. aureus is a Gram-positive coccus with a diameter of 0.5–1.5 μm, grouped as single cells, in pairs, tetrads, short chains, or forming a conglomerate in a cluster of grapes. This microorganism was first described in the year 1880, in Aberdeen, Scotland, by the surgeon Alexander Ágoston. The name comes from the Greek σταφυλόκοκκος, which is composed of the terms "staphylé," meaning cluster, and coccus, meaning grain or grape, and from the Latin "aureus" which means golden, that is to say "cluster of golden grapes."

They are non-motile bacteria, not sporulated, with no capsule (although there are some strains that develop a slime capsule); they are facultative anaerobes. Most staphylococci produce catalase (enzyme capable of dismutating hydrogen peroxide in $H_2O + O_2$), characteristic that is used to differentiate its sort from others like *Streptococcus* and *Enterococcus*. In 1961, the first report was made on the existence of a methicillin-resistant *Staphylococcus aureus* [18].

3.1 *Staphylococcus aureus* and endothelial cell

S. aureus is a pathogen that causes significant morbidity and mortality worldwide [2]. It is the leading pathogen associated with life-threatening bloodstream infections [19].

Although *S. aureus* is mainly known as an extracellular pathogen, it has been shown to invade and survive within endothelial cells, both within vacuoles and free in the cytoplasm, which implies that the bacteria can escape from the phagolysosome. *S. aureus* tends to infect endovascular tissue. It is believed that this ability contributes to causing a persistent endovascular infection with endothelial destruction.

3.2 Endothelial cell and *Staphylococcus aureus* ingestion

On the other hand, the death of endothelial cells after the invasion of *S. aureus* occurs at least in part by apoptosis, as demonstrated by DNA fragmentation and changes in nuclear morphology. Apoptotic changes are observed as early as 1 h after infection of endothelial cells [18]; they are considered to function as nonprofessional phagocytes, being able to ingest *S. aureus* [20, 21] following the adhesion of this to endothelial cell monolayers; invasion can occur through ingestion by endothelial cells.

For the internalization of *S. aureus*, adherence seems to be necessary, since the use of the phagocytosis inhibitor cytochalasin D prevented apoptosis. Studies show that living intracellular *S. aureus* induces apoptosis of endothelial cells and that this depends on a factor associated with viable organisms, since dead *S. aureus* (by ultraviolet light) also internalized does not induce it [18]. The process has been observed through electron transmission micrographs of bovine aortic endothelial cell monolayers infected with *S. aureus*, showing phagocytosis following a sequence of events: (I) adhesion of *S. aureus* to the endothelial cell, (II) formation of cup-shaped processes on the surface of the endothelial cell underlying the adherent bacteria, and (III) elongation of the cup and engulfment of bacteria within a phagosome [19].

3.3 Heme prosthetic group and *Staphylococcus aureus*

To colonize a vertebrate host, *S. aureus* requires numerous nutrients, such as the prosthetic group heme. The requirement can be met through two distinct mechanisms: importing exogenous heme through dedicated machinery or synthesizing endogenous heme from own metabolic precursors. These two mechanisms are necessary for a complete virulence of *S. aureus* [22, 23]. Once acquired, heme is used for several cell processes. The intact heme is used as a cofactor for enzymes [24], including cytochromes in the electron transport chain, catalase for the detoxification of reactive oxygen species, and bacterial nitric oxide synthase (bNOS).

Although the *S. aureus* requires heme, its excess is toxic to the germ, so it has a mechanism for hem detoxification through a hem sensor system (HssRS) that induces the expression of a hem regulator transporter (hrtAB) [25]. The suppression of the components of this route affects the virulence of *S. aureus*. This ability to detoxify heme is critical to survive in the host. Also, the synthesis of nitric oxide is important for the bacteria to survive. Bacteria encode genes similar to nitric oxide synthetase in mammals, which leads to the characterization of the nitric oxide synthase hemoprotein (bNOS) [26].

3.4 *Staphylococcus aureus* as a pro-inflammatory agent

The *S. aureus* contains molecules such as peptidoglycan and lipoteichoic acid, potent stimulants for the production of cytosines such as TNF-α, IL-4, IL-6, IL-8, IL-12, IL-1be, growth-regulated oncogene (GRO) alpha, and regulated upon activation, normal T-cell expressed, and secreted (RANTES). RANTES has a chemotactic function to perform leukocyte recruitment to areas of infection in addition to inducing tumor necrosis factor alpha and interleukin 1. Elevated levels can persist for 7–14 days [27]. As we can observe, *S. aureus* activates in a very important way the process of inflammation.

3.5 *Staphylococcus aureus* and blood stream infections in infective endocarditis

Circulatory blood stream infections (positive blood cultures) occur in patients with intravascular prosthetic devices as the most common source of infections related to health care [28]. MRSA was the most frequent pathogen in these types of infections with a consistent increase in the isolates of MRSA [29–31]. In the EU, epidemiological surveillance data on bloodstream infections show a marked variability among the member countries that make up a proportion of *S. aureus* that is resistant to methicillin, ranging from less than 1% to more than 50%. In addition to infections associated with health care, new MRSA strains have emerged in their communities as human pathogens associated with livestock [32].

3.6 Endocardial endothelium and myocardial capillary endothelium

The anatomical and physiological barriers of cardiac protection such as the endothelium can be compromised in its structure when areas of turbulence and injury are generated, producing an area exposed to infection. The intracardiac cavities have a cell layer called endocardial endothelium (EE) that covers the endocardium of the atria, ventricles, and all their anatomical components (papillary muscles, chordae tendineae, and heart valves). The EE acts as an active mechanism of biological heart-blood barrier, since it interacts dynamically with cardiomyocytes allowing direct communication and signaling between both types of cells. This

electrochemical communication between the cells of the EE and the cardiomyocytes allows a rapid intracellular electrochemical propagation and amplification of the functional properties of the EE.

Signaling between cardiac endothelial cells (EE and myocardial capillary endothelium) and cardiomyocytes influences cardiac growth, contractile performance, and rhythmicity. The network of Purkinje fibers and the subendocardial neural plexus (parasympathetic nervous system) is immediately below the endocardial endothelium (EE) and participates in the endothelial control of cardiac rhythm. Endothelin-1 (Et-1), nitric oxide (ON), prostaglandins (PGI2), prostacyclin (AI and AII), angiotensin I and II, and vascular endothelial growth factor (VEGF) are involved in these processes.

The endothelium that covers cardiac structures is at the vascular level, the myocardial capillary, and the endocardium; its activation includes changes in the endothelial phenotype as part of the physiological adaptive response to several possible injuries and stressors. The dysfunction of the endothelium implies a deregulated response that is not useful and that can be permanent.

One of the clinical disorders that selectively damage the endocardium and subendocardial interstitial tissue is endocarditis. This entity causes activation of the vascular and endocardial endothelial system, as well as poor adaptation or failure characterized by hemodynamic abnormalities, neurohormonal imbalance, cytokine expression, and endothelial dysfunction [33].

Infective endocarditis is an anatomoclinical entity characterized by microbial infection of the valvular or parietal endothelium or both; it is located predominantly on the left side of the heart, although it can also occur in the right (e.g., endovenous drug), which produces inflammation, exudation, and proliferation of the endocardium. The most characteristic lesion is the vegetation, constituted by an amorphous mass of platelets and fibrin, of variable size, which contains multiple microorganisms and scarce inflammatory cells (fibrinoplaquetary thrombus) [34]. This type of lesions generates metastatic infection in other anatomical territories, for example, the central nervous system, apostematous meningitis, myocarditis, pyelonephritis, and splenic abscesses which are at risk of rupture [35, 36].

4. Clinical manifestations

The clinical manifestations of infective endocarditis are acute rapidly progressive or subacute; the pathophysiological processes of both are explained by immunological and vascular phenomena, such as inflammatory response, mediators of inflammation triggered by a maladaptive response to an infectious process, aggregation of immune complexes, infectious vasculitis, and peripheral microembolism [34, 37]. Depending on the affected cardiac cavity (right/left) or valvular system, the clinical manifestations will be due to the aforementioned processes [38] (**Table 1**).

4.1 Anatomopathological changes

The anatomopathological changes due to the formation of vegetations in the valvular ring and/or in the leaflets cause an anatomical alteration. If this anatomical alteration generated by a vegetation prevents valvular closure, it will be expressed as a murmur of valvular insufficiency and in severe cases such as microembolisms septic and non-septic and cardiac failure [34, 37].

	Patients, %
Sign	
Fever	86–96
New murmur	48
Worsening of old murmur	20
Hematuria	26
Vascular embolic event	17
Splenomegaly	11
Splinter hemorrhages	8
Osler nodes	3
Janeway lesions	5
Roth spots	2
Complication	
Stroke	17–20
Non-stroke embolization	23–33
Heart failure	14–33
Intracardiac abscess	14–20
New conduction abnormality	8

Murdoch et al. [38].

Table 1.
Clinical signs and complications of infective endocarditis.

4.2 Considerations on the cardiac cavity affected by infective endocarditis

The standard reference to corroborate the clinical diagnosis of IE is transesophageal echocardiography since the transthoracic echocardiogram, even when limited to native valves, decreases the diagnostic probability of IE [39].

Right and left endocarditis are two distinct entities that require different clinical and surgical approaches. The diagnosis of endocarditis on the right side requires a high index of clinical suspicion. It can occur with a history of intravenous drug use, fever, and pulmonary infiltrates, although intravenous drug abuse is also a cause of IE on the left side of the heart [36]. The information provided by echocardiography is of prognostic and therapeutic value.

If the vegetation is <1.0 cm in diameter, it can be expected that antibiotic therapy will resolve the infection; if the size of the vegetation determined by echocardiography is ≥1.0 cm without response to treatment, surgical intervention should be considered [40].

Surgical treatment in IE on the left side of the heart, for example, the mitral valve, is indicated in patients with severe mitral regurgitation, even in the absence of congestive heart failure, with mitral annular abscess, large vegetation >10 mm, uncontrolled sepsis, and multiple embolisms [41]. Mitral valve (MV) replacement has traditionally been considered as the standard treatment for MV endocarditis that does not respond to antibiotic treatment.

However, the pioneering work of Dreyfus et al. surgery for repair of the mitral valve with IE can be performed safely and is often associated with a better outcome compared to mitral valve replacement [42, 43].

5. Role of immunogenetics in the physiopathology of sepsis and infective endocarditis

5.1 Introduction

It has been largely recognized that infective processes have considerably different patient-to-patient behavior in such a way that some patients respond well to the treatment applied and some others end up developing a dysregulated immune response known as sepsis [44], organ failure, and some even die from this process. Infective endocarditis does not escape from this fact. Many variables, such as the virulence of the pathogen and the quality of the treatment applied, among many others, participate in an additive manner to conform the clinical outcomes of infections, and this helps to understand why a patient takes the road of success or failure regarding the control of the septic process. One of the most recent advances in the understanding of the pathophysiology of infective processes, including infective endocarditis, is the demonstration that genetically determined differences in the immune system of individuals are one of these many factors that determine the phenotypic behavior and outcomes. Therefore, the next chapter section is dedicated to explaining the existing evidence of the participation of immunogenetics in the development of infective endocarditis and sepsis.

Recently, the concept of sepsis has been redefined as the result of a better understanding of its pathophysiology, particularly regarding the early activation of pro- and anti-inflammatory immune responses. As the third international consensus definition of sepsis states, sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to an infection [45]. Then, if sepsis is dependent on a dysregulated response, and this response is executed principally by the host immune system, then genetically defined differences between individuals immune system might play a role in the genesis of this syndrome and at least partially explain why some patients take the road of sepsis and some others do not. This hypothesis had long been existed, but it was until 1988 that the theory started gaining scientific evidence of its existence, when Sørensen et al. [46] published what is considered a landmark study with respect to this topic. In this article, the authors studied the genetical influences on the principal causes of nonviolent premature death in the Danish population; to separate them from the environmental influences, they studied a selected group of people that had been adopted early in life. This was extracted from the Danish Adoption Registry and included adoptees that were born between 1924 and 1926. They traced them up and demonstrated that the death of a biologic parent from an infection before the age of 50 resulted in a relative risk of death from infective causes in the adoptees of 4.5. Since this publication, a great number of studies have been conducted in an attempt to define the specific genetic variations that determine these differences in outcome. This task has resulted complex; as both pro- and anti-inflammatory responses contribute to the outcome of septic processes, all genes encoding effector proteins in the biochemical pathways of the inflammatory response to infection are potential candidates to determine the genetical background responsible for the interindividual differences aforementioned [47].

5.1.1 The study of single nucleotide polymorphism associations with sepsis and IE outcomes.

The most studied specific type of genetic anomaly regarding to sepsis susceptibility is the single nucleotide polymorphism (SNP); therefore, the largest body of evidence comes from the study of this type of genetic variations. SNPs are defined as frequent (occurring in >1% of the population) variations in the human DNA

sequence [48] and consist in the exchange of a single base pair for another in a specific location in the DNA sequence. They may occur within the exonic (coding) or intronic (noncoding) region of the gene and can have different consequences which include alteration of expression or structure of proteins and enzymes, introduction of an alternative translation initiation codon or stop codon, and destabilization of exonic mRNA [49]. Methodologically speaking, most studies are association studies (case/control and cohort type), and two approaches have been done. In the most common approach (which for purposes of this chapter section are going to be called specific SNP association studies), the frequency of one or more known SNPs present in genes coding defined molecular candidates involved in the pro- or anti-inflammatory responses (e.g., alpha tumoral necrosis factor gene) is compared between a specific phenotypically defined interest group (patients with a confirmed specific infectious scenario as sepsis or IE) and a control group, usually consisting of a group of healthy blood donors ideally with an ethnicity equal to the interest group. If there are statistically significant differences in the frequency of the SNPs between groups, authors take this as proof that such genetic differences are implicated in the specific way that the study population responds to infection. The other approach is a type of study called genome-wide association studies (GWAS). As the previously described type of study, GWAS are association studies (most frequently case–control studies) but differ in that the frequency of most known SNPs is measured in the whole genome of the cases (infected group) and controls (healthy blood donors). When a statistically significant difference is found, authors take this as proof that such genetic variability is responsible for the difference in outcomes and then hypothesize, based in the location of the SNPs, about the biological plausibility of the association given the gene that is affected.

5.2 The evidence in sepsis

A large number of specific SNP association studies have been conducted respecting the most important effector molecules in response to sepsis and also some GWAS.

5.3 Tumor necrosis factor alpha

In response to an infectious stimuli, such as lipopolysaccharides (LPS), tumor necrosis factor α (TNF-α) is a cytokine that is released early mainly by macrophages, and it is a principal mediator of the inflammatory response to infection which stimulates acute inflammation by its action on different cells, such as endothelial cells and leukocytes [50].

Many studies have been done in an attempt to determine if specific SNPs in the TNF alpha factor gene are implicated in sepsis susceptibility with conflicting results. A recent meta-analysis from Zhang et al. [51] which included 23 articles that evaluated the effects of TNF-α rs1800629 and rs361525 polymorphisms on sepsis risk found that TNF-α rs1800629 was associated with increased sepsis risk in the overall population in four genetic models, including adenosine (A) vs. guanine (G) ($p < 0.001$, odds ratio (OR) = 1.32), GA vs. GG ($p < 0.001$, OR = 1.46), GA + AA vs. GG ($p < 0.001$, OR = 1.46), and carrier A vs. carrier G ($p < 0.001$, OR = 1.32). These results suggest an implication of these genetic variations with an increased susceptibility for sepsis development.

5.4 Tumor necrosis factor beta (TNF-β)

TNF-β is a cytokine produced by T lymphocytes similar to TNF-α and binds to TNF receptors. It activates endothelial cells and neutrophils and is a mediator of

acute inflammatory response, providing a link between T-cell activation and inflammation. These effects are the same as those of TNF-α, consistent with their binding to the same receptors. However, as the quantity of TNF-β is much less than that of TNF-α made by lipopolysaccharide-stimulated mononuclear phagocytes, TNF-β is not readily detected in the circulation. For this reason, TNF-β is usually a local cytokine and not a mediator of systemic injury. A single nucleotide polymorphism has been found at position +252 in the first intron of the TNF-β gene and consists of a G in the wild-type allele (TNFB1) and an A in the variant allele (TNFB2). Known as the Nco1 polymorphism, it has been proposed as a potentially influential locus in many inflammatory conditions. Delongui et al. studied the association of the TNF-β Nco1 genetic polymorphism with susceptibility to sepsis in 60 patients diagnosed with sepsis and in 148 healthy blood donors. Among the septic patients, the allelic frequencies of TNFB1 and TNFB2 were 0.2833 and 0.7166, respectively, and they differed from those observed in the blood donors ($p = 0.02$). The TNFB2 allele frequency was higher in the septic patients than in the controls [OR = 1.65 (CI 95% 1.02–2.69), $p = 0.0315$], all this suggesting an implication in susceptibility to sepsis [52].

5.5 Interleukin 10 (IL-10)

IL-10 has beneficial anti-inflammatory properties; however, an excess of IL-10 has been reported to induce immunosuppression in bacterial sepsis. Published data demonstrates that lower production of IL-10 from stimulated peripheral blood mononuclear cells (PBMC) from septic patients is significantly correlated with favorable disease outcome [53]. Stanilova et al. [54] investigated the −1082 (A/G) polymorphism in the promoter of the IL-10 gene by measuring IL-10 production from stimulated peripheral blood mononuclear cells (PBMC) and to evaluate the relationship of this polymorphism with susceptibility to severe sepsis and its outcome. They found that carriage of at least one copy of IL-10-1082 G allele in sepsis patients and in healthy controls resulted in a statistically significant increase in IL-10 production from stimulated PBMC. Patients who survived sepsis had a significant decrease of IL-10-1082 allele G frequency, compared with controls (17 vs. 47.2%; $p = 0.012$). This suggests that this genetic variation has an impact in IL-10 production and in the outcomes of septic patients [55].

5.6 Interleukin-1 receptor antagonist gene (IL-1 Ra)

Interleukin 1β (IL-1β) is a potent pro-inflammatory cytokine implicated in the development of chronic inflammatory disorders. IL-1β signaling is blocked by IL-1 Ra, a natural regulator of IL-1 cytokines. IL-1 Ra binds to the IL-1 receptor and thereby prevents binding of both IL-1a and IL-1b [56]. F. Arnalich et al. aimed to determine the influence of the polymorphism within the intron 2 of the IL-1RNa (IL-RNa*) on the outcome of severe sepsis. A group of 78 patients with severe sepsis (51 survivors and 27 non-survivors) was compared with a healthy control group of 130 blood donors and 56 patients with uncomplicated pneumonia. They found a significant association between IL-1RN* polymorphism and survival. After adjusting for age and APACHE II score, they did a multiple logistic regression analysis that showed that patients' homozygotes for the allele *2 had 6·47 times more risk of death (95% CI 1·01–41·47, $p = 0.04$). These authors concluded that these genetic mutations might be implicated in an increased risk of death in septic patients [57].

5.7 High-mobility group box 1 protein (HMGB1)

HMGB1 is a pleiotropic cytokine that has been implicated in the pathophysiology of systemic inflammatory response syndrome (SIRS) and sepsis. HMGB1 is measurable in the systemic circulation in response to severe injury. This protein has the propensity to bind to a variety of inflammatory mediators such as lipopolysaccharide and pro-inflammatory cytokines, including IL-1. The role of HMGB1 as an endogenous molecule facilitates immune responses and has an important role in homeostasis between tissue and disease. HMGB1 is implicated in the pathophysiology of a variety of inflammatory diseases, and it has been found that variation in the HMGB1 gene is associated with mortality in patients with systemic inflammatory response syndrome [58]. Kornblit et al. performed a long-term, 4-year study comparing HMGB1 sequencing data in 239 intensive care unit (ICU) patients with HMGB1 blood levels and clinical outcomes. The promoter variant −1377delA was associated with a markedly reduced long-term survival rate after ICU admission in SIRS patients. There was also a significant interaction with a polymorphism within the coding region of the HMGB1 gene at position 982 (C > T) in exon 4; carriers had an increased frequency of early death from infection [59].

5.8 Toll-like receptor 2 (TLR2)

TLRs are a group of pattern recognition receptors. They play important roles in regulating inflammatory reactions and activating adaptive immune response to eliminate infective pathogens [60]. TLR2, a key member of TLR family, can recognize a variety of bacterial lipoproteins. The mechanism of TLR2-recognizing lipoproteins has been elucidated; after TLR2 recognizes lipoproteins, it activates MyD88 adaptor-like protein and initiates a signaling pathway, which induces further immune response [61]. This evidence puts TLR2 gene as an appealing candidate for determining sepsis risk. In a recent meta-analysis, Gao et al. [62] analyzed a total of 12 studies (11 records) with 898 cases and 1517 controls examined to determine the association between the TLR2 Arg753Gln polymorphism and sepsis risk. The combined results of the overall comparison indicated that there were significant associations between the TLR2 Arg753Gln polymorphism and sepsis risk under the allele comparison model and the dominant model, respectively (for A vs. G, OR 1.76, 95% CI 1.05–2.95, p = 0.03; for AA/GA vs. GG, OR 1.92, 95% CI 1.11–3.32, p = 0.02).

5.9 Genome-wide association study

Rautanen et al. [63] did a genome-wide association study in three independent cohorts of white adult patients admitted to ICU with sepsis, severe sepsis, or septic shock due to pneumonia or intra-abdominal infection (n = 2534 patients). The primary outcome was 28-day survival. Results for the three cohorts of patients with sepsis due to pneumonia were combined in a meta-analysis of 1553 patients. The most significantly associated SNPs were genotyped in a further 538 white patients with sepsis due to pneumonia (an independent fourth cohort), of whom 106 died. In the genome-wide meta-analysis of three independent pneumonia cohorts, common variants in the FER gene were strongly associated with survival (p = 9·7 × 10–8; OR 0·52 [95% CI 0·41–0·66]). Genotyping of the additional fourth cohort strengthened the evidence for association with survival (p = 5·6 × 10–8; OR 0·56 [0·45–0·69]).

5.10 The evidence in infective endocarditis

There are many risk factors described for the development of IE; nevertheless up to 30–50% of patients with this diagnosis does not have any known risk factor [64]. Therefore, as in sepsis per se, there is thought to be immunogenetic influences that affect the risk of development and outcomes in IE. However, in comparison to sepsis, evidence of the immunogenetic influence on the susceptibility and outcomes of IE is less robust. Golovkin et al. [65] hypothesized that inherited variation in TLR and triggering receptor expressed on myeloid cells (TREMs) genes may affect individual susceptibility to IE. They conducted a specific SNP study in which the distribution of genotypes and alleles of the TLR1, TLR2, TLR4, TLR6, and TREM-1 gene polymorphisms was investigated in 110 Caucasian subjects with IE and 300 matched healthy blood donors. ORs with 95% CI were calculated. They found that C/C genotype of the rs3775073 polymorphism within TLR6 gene was associated with a decreased risk of IE (OR = 0.51, 95% CI = 0.26–0.97, p = 0.032) according to the recessive model; however, there was no association between the other investigated SNPs within TLR andTREM-1 genes and IE.

Moreau et al. [66] conducted a GWAS of 67 patients with definite native valve *S. aureus* IE (cases) and 72 matched native valve patients with *S. aureus* bacteremia but without IE (controls). Unfortunately, no SNPs were significantly associated with *S. aureus* IE at the genome-wide level ($p < 5 \times 10^{-8}$). Four suggestive SNPs ($p < 0.00001$) were located on one locus on chromosome 3, near the genes CLDN11 and SLC7A14. For all, the frequency of the minor allele was lower in cases than in controls, suggesting a protective effect against *S. aureus* IE. The same association was observed using an independent Danish verification cohort of *Staphylococcus aureus* bacteremia with (n = 57) and without (n = 123) IE. An ex vivo analysis of aortic valve tissues revealed that *S. aureus* IE associated SNPs mentioned above were associated with significantly higher mRNA expression levels of SLC7A14, which is a cationic amino acid transporter protein. These results suggest an IE-protective effect of SNPs on chromosome 3 during *S. aureus* bacteremia. The authors concluded that the effects of protective minor alleles may be mediated by increasing expression levels of SLC7A14 in valve tissues.

6. Inflammation and oxidative stress

The modern mitochondria have an evolution of more than a billion years, originating as an invading *Eubacterium* in early eukaryotic cells. The knowledge of the structure, functionality, and the similarities of the DNA between mitochondria and bacteria strongly prove the endosymbiotic origin of the mitochondria. Of the 1000 or more mitochondrial proteins, only 13 are encoded by the mitochondrial genome, the rest is transcribed and translated into the nuclear genome and transported to the inner mitochondrial membrane [67].

In the heart the populations of mitochondria include subsarcolemmal mitochondria, which are more susceptible to injury. Subsarcolemmal mitochondria provide energy for membrane-related processes, including signal transduction, ion exchange, and substrate transport, whereas the intermyofibrillar mitochondria more directly support muscle contraction [68].

The mitochondrial oxidative phosphorylation process is responsible for the conversion of macronutrient energy (e.g., glucose, fatty acids, and amino acids) into ATP through a set of coordinated and highly coupled reactions where the macronutrients are oxidized and the oxygen is reduced to water and adenosine diphosphate (ADP) is phosphorylated to ATP.

6.1 Chemiosmotic hypothesis

In the chemiosmotic hypothesis [69], the proton gradient is formed by removing H^+ from the interior (matrix), while the negative charges remain inside, largely as OH^- ions; the pH on the outer face of the membrane (intermembrane space) can reach a pH of 5.5, while the pH just at the inner side (matrix) of the same can reach 8.5; this gradient is 3 pH units. Recall that the pH is equal to - log. of $[H^+]$, and therefore 3 units of pH mean that the $\Delta H^+ = 1000$ between both faces of the membrane, that is to say there are 1000 times more H^+ in the intermembrane space than on the side of the membrane that is in contact with the mitochondrial matrix (**Figure 1**).

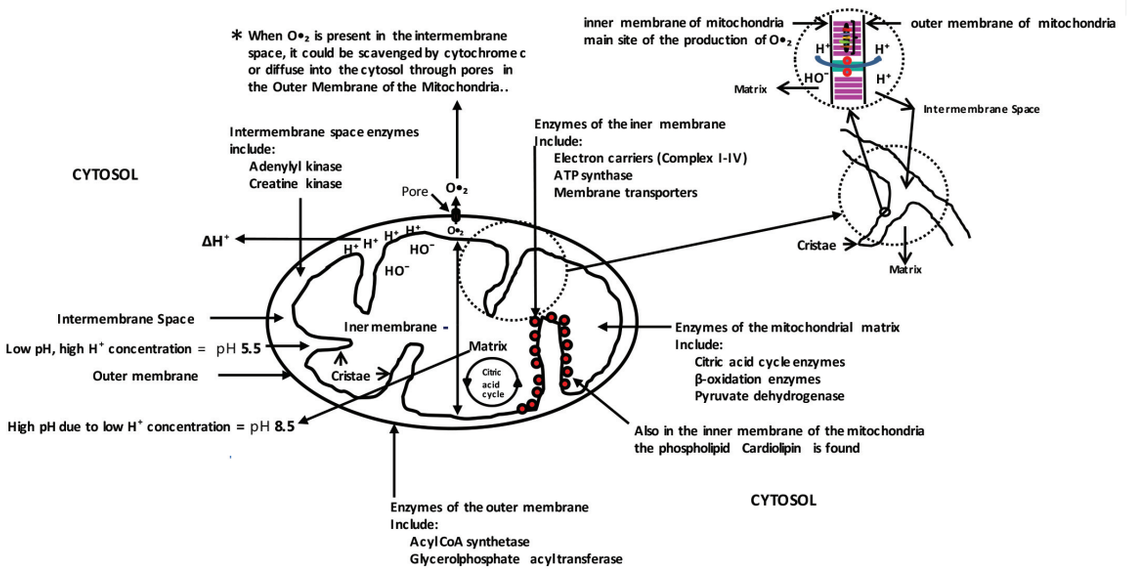

Figure 1.
The creation of a proton gradient (ΔH^+) in the intermembrane space is produced by the chain of electron transport and the synthesis of ATP synthase, which is maintained by the electrons that pass from the reducing equivalents (NADH, FADH2) to the cytochromes along the inner membrane of the mitochondria. ATP synthase uses that gradient to generate ATP. The two processes are associated with the inner membrane of the mitochondria in the mitochondrial crests. Note that the enzymes of the citric acid cycle and β-oxidation are contained in mitochondria, together with the respiratory chain, which collects and transports reducing equivalents, directing them to their final reaction with oxygen to form water, and the machinery for oxidative phosphorylation, the process by which the liberated free energy is trapped as high-energy phosphate. Source: Botham and Mayes [70].

The process begins when carbon substrates enter the tricarboxylic acid cycle through acetyl CoA or anaplerotic reactions. Oxidation of these substrates generates reducing equivalents in the form of NADH and FADH2, which provide electron fluxes through the complexes of the respiratory chain, complex I (NADH dehydrogenase) and complex II (succinate dehydrogenase). The flow of electrons through complexes I and II converges in complex III (ubiquinone-cytochrome c reductase), together with electrons from electron transfer flavoproteins (beta oxidation), although the mobile electron carrier coenzyme Q as second mobile electron carrier transfers electrons to the IV complex (cytochrome c oxidase) where they are finally transferred to oxygen, producing water. A gradient of protons (an electrochemical gradient) through the inner mitochondrial membrane is generated by the action of electron transport through complexes I, III, and IV. The potential energy of this gradient is exploited by the V (ATP synthase) complex to phosphorylate ADP to ATP [71]. It is clear that the maintenance of the mitochondrial membrane potential through the transport of electrons is critical for the proper function of the organelle and, therefore, of the cell and of ascending form of organs and systems.

6.2 Reactive oxygen species

In the process of mitochondrial respiration, the generation of reactive oxygen species (ROS) is generally a cascade of reactions that begins with the production of superoxide $O\bullet_2$. The oxidative stress is defined as an imbalance that favors ROS production on antioxidant defenses; most ROS are products of mitochondrial respiration. Approximately 1–2% of the molecular oxygen consumed during the process of mitochondria respiration is converted to superoxide radicals. Briefly, the reduction of an electron of molecular oxygen produces a relatively stable intermediate, the superoxide anion ($O\bullet_2$); the importance of this is that it serves as the precursor to most ROS.

Therefore, it is very important to take into account the sources that generate it. There is evidence that most of the $O\bullet_2$ generated by intact mammalian mitochondria in vitro is produced by complex I. The production of superoxide—$O\bullet_2$—is mainly carried out in the inner mitochondrial membrane (IMM) together with complex III [72, 73]. On the other hand, the production of $O\bullet_2$ is stimulated by the presence of succinate (substrate of complex II) [74]. Ubiquinone as part of the respiratory chain binds complexes I with II and II with III which is also important for the formation of $O\bullet_2$ by complex III [75]. Oxidation of ubiquinone—Q cycle—and unstable semiquinone also generates $O\bullet_2$ (**Figure 2**).

The Q cycle couples electron transfer to proton transport in complex III electrons are passed from QH_2 to cytochrome c via complex III (Q-cytochrome c oxidoreductase) as described in **Figure 2**.

$$QH_2 + 2\text{cyt } c_{\text{oxidized}} + 2H^+ \text{ matrix} \quad (1)$$

$$Q + 2\text{cyt } c_{\text{reduced}} + 4H^+ \text{ intermembrane space} \quad (2)$$

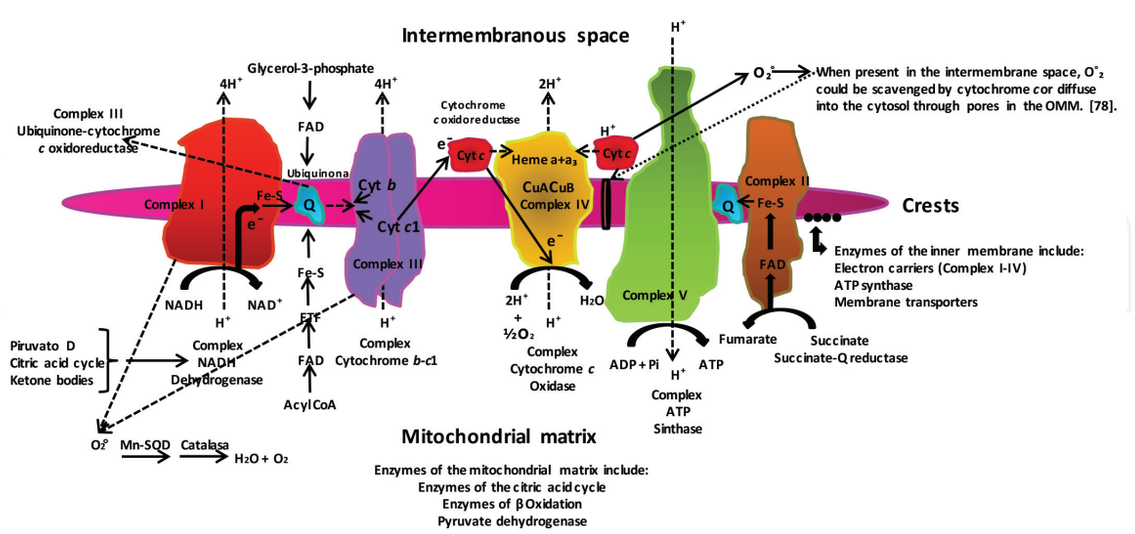

Figure 2.
The flavin adenine dinucleotide (FAD) can be reduced in reactions involving the transfer of two electrons (to form $FMNH_2$ or $FADH_2$), but they can also accept one electron to form the semi Quinone. Electron-transferring flavoprotein (ETF). Fe-S, iron–sulfur proteins (nonheme iron proteins). The Fe-S take part in single-electron transfer reactions in which one Fe atom undergoes oxidoreduction between Fe^{2+} and Fe^{3+}. Coenzyme Q (Q) (also called ubiquinone) (complex I). Cytochrome c, Q-cytochrome c oxidoreductase (complex III), which passes the electrons on to cytochrome c; and cytochrome c oxidase (complex IV), which completes the chain, passing the electrons to O_2 and causing it to be reduced to H_2O. Q and cytochrome c are mobile. Q diffuses rapidly within the membrane, while cytochrome c is a soluble protein. Mn-SOD, manganese superoxide dismutase.

Superoxide rapidly dismutates into hydrogen peroxide spontaneously or at a low pH is catalyzed by superoxide dismutase. Other elements in the cascade of ROS generation are small molecules derived from oxygen, like the following: hydroxyl (OH•), peroxyl ($RO•_2$), and alkoxyl (RO•) and certain non-radicals that are oxidizing agents and/or are easily converted to radicals, such as hypochlorous acid (HOCl), ozone (O_3), singlet oxygen ($½O_2$), and hydrogen peroxide (H_2O_2). Nitrogen-containing oxidants, such as nitric oxide (NO), are called reactive nitrogen species (RNS), and the Fenton reaction catalyzed by iron leads to the generation of hydroxyl radical [76, 77]. The dismutation of superoxide anions by superoxide dismutases results in the production of H_2O_2. The mitochondria contribute 20–30% of the stable cytosolic concentration of H_2O_2 [78]; the subsequent interaction of H_2O_2 and $O•_2$ in a Haber-Weiss reaction, or the cleavage of H_2O_2 driven by Fe^{2+}-(or Cu^{2+}), can generate the highly reactive hydroxyl radical (OH•).

The Haber-Weiss reaction [79] may occur as a consequence of oxidative stress. The reaction is catalyzed by the iron in oxidation state (III); the first step of the catalytic cycle is produced by the reduction of the ferric cation to ferrous cation:

$$Fe_3{}^{+} + •O^{-}{}_2 \rightarrow Fe_2{}^{+} + O_2 \quad (3)$$

The second step is a reaction from Fenton:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{-} + •OH \quad (4)$$

6.3 Superoxide dismutases

Briefly, superoxide dismutases (SOD) are a group of metalloenzymes (containing Fe, Mn, or Cu and Zn) that catalyze the disproportionation of superoxide free radical (2O•) to form hydrogen peroxide and oxygen as shown below:

$$2•O_2 + 2H^{+} \Leftrightarrow H_2O_2 + O_2 \quad (5)$$

In some cell types, CuZnSOD is present in the mitochondrial intermembrane space, where it can convert $O•_2$ to H_2O_2, thus permitting further diffusion into the cytosol.

Superoxide rapidly dismutates into hydrogen peroxide spontaneously or at a low pH is catalyzed by sequential actions of superoxide dismutase (SOD), and catalase converts superoxide into oxygen and water. Other elements in the cascade of ROS generation are small molecules derived from oxygen, which also include oxygen radicals [80].

Because ROS are biologically damaging, they need to be metabolized to prevent the damage they can cause when interacting with other compounds, for which the cell counts with mechanisms that avoid it like SOD. However, when the formation of ROS increases, they have the capacity to deteriorate mitochondrial function and jeopardize cell survival in different ways, where the mitochondrion seems to be responsible for regulating apoptosis [81]. ROS are a major threat to encode, transfer, and transport electrons and generate ATP by directly damaging mitochondrial DNA (mtDNA) which encodes 13 polypeptides, 12 transfer RNAs (tRNAs), and 2 ribosomal RNAs (rRNAs). All of them are essential in the chain of transport of electrons for the production of ATP, so when interacting with them, oxidative phosphorylation and therefore energy genesis is compromised [67]. ROS, and the release of proapoptotic proteins from the intermembrane space of mitochondria, triggers the activation of cell death.

7. Nicotinamide adenine dinucleotide phosphate oxidase

7.1 NADPH oxidase

The heart has the highest oxygen uptake rate in the human body, and the oxygen consumption is normally 8–13 mL 100 g^{-1} min^{-1} at rest [82]. The cellular sources in the genesis of ROS in the heart include cardiac myocytes, endothelial cells, and neutrophils. Within cardiac myocytes, ROS can be produced by several mechanisms, including the transport of mitochondrial electrons, NADPH oxidase (nicotinamide adenine dinucleotide phosphate oxidase), and xanthine dehydrogenase/xanthine oxidase. To meet the high demand for ATP synthesis, cardiac myocytes therefore have the highest volume density of mitochondria in the entire human body.

NADPH oxidase with its isoforms generically called NOX is the major source of ROS (reactive oxygen species) in biological systems. NOX proteins are involved in a plethora of pathophysiological conditions, so it is important to note that the functions of NOX proteins in different tissues are influenced by the activity of other oxidases and peroxidases, such as myeloperoxidase, xanthine oxidase, and hemoxygenase [83].

In the heart, the cardiomyocyte NADPH oxidase seems to be the main source of production of ROS from the heart in failure [84, 85].

NADPH oxidases are present in phagocytes and in a wide variety of non-phagocytic cells. NADPH generates superoxide by transferring electrons from NADPH into the cell through the membrane and coupling them to molecular oxygen to produce superoxide anion. Structurally, NADPH oxidase is an enzyme that has several components: it includes two integral membrane proteins, the glycoprotein gp. 1 Phox and the adapter protein p22 (phox), which together form the heterodimeric b558 flavocytochrome that form the nucleus of the enzyme. During the resting state, the multidomain regulatory subunits p40P (phox), p47 (phox), and p67 (Phox) are located in the cytosol organized as a complex. Activation of phagocytic NADPH oxidase occurs through a complex series of protein interactions.

The products that activate it are angiotensin II, endothelin-1, TNF-α, and mechanical forces. The cardiomyocyte NADPH oxidase and any other NADPH oxidase when stimulated generates large amounts of ($O•_2$), which dismutes to H_2O_2; both in the tissue presence of iron and H_2O_2, increase the production of ROS, lead to the production of the HO• radical; these are highly reactive and can induce peroxidative damage of molecules within reach such as lipids, proteins, carbohydrates, nucleic acids, and membranes, resulting in the increase of reactive substances thiobarbituric acid (TBARS) in patients with heart failure.

This suggests that some pro-inflammatory products can activate a pathway to generate oxidative stress damage through the NADPH oxidase and increase the biological damage to the heart by ROS which correlates with left ventricular dysfunction [86]. Even more, the fact that NADPH oxidase is activated by pro-inflammatory products suggests a link with the genesis of oxidative stress.

Of the infectious processes in the heart on the balance of oxidants and antioxidants in the myocardium little is known. IE in which heart valves are usually affected, generating refractory congestive heart failure, is accompanied by a very important inflammatory response, both local and systemic with high circulating concentrations of IL-6, IL-2R, and IL-1β [87]. In the case of infective endocarditis, the interaction of the infectious agent and its products (chemotactic, formylated, and lipopolysaccharide peptides) with monocytes and polymorphonuclear cells can

increase the production of ROS through the activation of NADPH oxidase, secondary to the inflammatory state.

IE induces an increase of pro-inflammatory cytokines, being able to stimulate ROS production in the myocardium and peroxidative damage to several molecules. The substances reactive to thiobarbituric acid (TBAR), in a study comparing cardiac tissue from patients with IE and patients with valvular heart disease (VHD) of rheumatic etiology; TBARs were increased 10 times more in IE than their controls with VHD [88].

8. Inducible nitric oxide synthase

In sepsis, endotoxins and cytokines stimulate the expression of inducible nitric oxide synthase (iNOS) and the overproduction of nitric oxide (NO) in various tissues; it also stimulates the excessive activity of NADPH oxidase that facilitates the expression of iNOS to produce large amounts of NO. The NADPH oxidases derived from ROS by activating the Jak2-IRF1 and JNK-AP1 pathways are necessary for the induction of iNOS. The main mechanism that regulates the activity of iNOS is the modulation of the transcription of the iNOS gene. The NO derived from iNOS and its metabolite peroxynitrite can contribute to the pathological alterations observed in sepsis, such as endothelial dysfunction, hypotension, and multiple organ failure [89].

The peroxynitrite anion $ONOO^-$

$$H_2O_2 + NO_2^- \rightarrow ONOO^- + H_2O \quad (6)$$

$$\bullet O_2^- + \bullet NO \rightarrow ONO_2^- \quad (7)$$

9. Metabolome and proteome

The composition of metabolites such as amino acids, intermediate products of the Krebs cycle, and acylcarnitines (metabolome) and protein complement expressed in cells, tissues, or body fluids (proteome) of survivors of sepsis and non-survivors was analyzed in patients who studied with sepsis by three different pathogens, *S. pneumoniae*, *S. aureus*, or *E. coli*. The main differences between survivors and non-survivors were those highlighted in their metabolome and proteome. For example, nine proteins involved in the transport of fatty acids were decreased in non-survivors of sepsis, suggesting a defect in β-oxidation. The nonacceptance and nonuse of fatty acids by the mitochondria led to an accumulation of acylcarnitines in the plasma; another predictive marker is that glycolysis and gluconeogenesis were also markedly different. Survivors of sepsis showed decreased levels of citrate, malate, glycerol, glycerol 3-phosphate, phosphate, and glucogenic and ketogenic amino acids, while non-survivors showed elevated levels of citrate, malate, pyruvate, dihydroxyacetone, lactate, phosphate, and gluconeogenic amino acids [90]. That is to say that the pathways for the transport of fatty acids, as well as glycolysis and gluconeogenesis, are damaged, so the substrate is low, and they are not used by the mitochondria.

10. Acetylome

Acetylome analysis identified a subpopulation of mitochondrial proteins that was sensitive to changes in the NADH/NAD+ ratio. Hyperacetylation induced by

mitochondrial dysfunction is a positive regulator of pathological remodeling in the heart of mice with *primary or acquired* mitochondrial dysfunction, as well as in humans with heart failure. Hyperacetylation of mitochondrial malate–aspartate shuttle (MAS) proteins impaired the transport and oxidation of cytosolic NADH in the mitochondria, resulting in altered cytosolic redox state and energy deficiency. Furthermore, acetylation of oligomycin-sensitive conferring protein at lysine-70 in adenosine triphosphate synthase complex promoted its interaction with cyclophilin D and sensitized the opening of mitochondrial permeability transition pore. There are two different mechanisms that point to the proteins of hyperacetylation, i.e., MAS and the regulators of mitochondrial permeability transition pore (mPTP), which mediate an increase in heart failure. Both could be fixed by normalizing the NAD+ redox balance either genetically or pharmacologically [91].

11. *Q* and cytochrome *c*

Q and cytochrome *c (*Cyt*c*) are mobile. *Q* diffuses rapidly within the membrane, while cytochrome *c* is a soluble protein that contains a peptide sequence located at the C-terminus of the protein [92] that allows it to cross the cell membranes in a nontraditional way. This property of Cyt*c* was used in a study in mice, which were subject to ligation and cecal puncture; they underwent sepsis and damage to mitochondrial respiration, which was restored with the injection i.v. of Cyt*c* [93]. The treatment led to an uptake of Cyt*c* into the cardiomyocytes, and survival increased from 15% for the sepsis control group to about 50% in mice that were also injected with Cytc [94].

12. Deregulated apoptosis and multiple organ failure

The death of cells of the immune system by deregulated apoptosis contributes to the dysfunction of the immune system and multiple organ failure (MOF) which is observed in sepsis. The immune cells most affected by this dysregulated apoptotic cell death appear to be lymphocytes [95]. Extensive lymphocytic apoptosis mediated by caspase-3 in sepsis may contribute to impaired immune response in septic patients [96]. Lymphocyte loss occurs by both death receptor and mitochondrial-mediated apoptosis, suggesting that there may be multiple triggers for lymphocyte apoptosis [97, 98].

Apoptosis in the immune system is a pathological event in sepsis which has been considered a therapeutic goal. Studies on sepsis in experimental animals suggest that the loss of lymphocytes during sepsis may be due to deregulated apoptosis and that it appears to be secondary to a variety of mediators that carry out both "intrinsic" and "extrinsic" cell death pathways.

In experimental animals, lymphocyte apoptosis is frequently seen 12 h after the onset of experimental polymicrobial sepsis in the thymus, spleen, and lymphoid tissues associated with the intestine. It has been suggested that deregulated lymphocytic apoptosis results in reduced septic survival through loss of lymphocytes, resulting in multiple organ failure and ultimately death. Lymphocyte apoptosis in the thymus appears to occur 4 h after the onset of sepsis and is independent of the effects of endotoxin or death receptors. Apoptosis in the spleen appears to be particularly important in mortality from sepsis, by an increase of the splenic apoptosis of lymphocytes in experimental animals after the cecal ligation and puncture (CLP) which results in a reduced survival [99].

In septic humans apoptosis does not seem to be generalized, since in these patients only extensive lymphocytic apoptosis was demonstrated, which suggests a damaged immune response, suggesting that other mechanisms apart from cell death participate in the conditions associated with mortality [100]. For example, hyperglycemia induces the expression of leukocyte adhesion molecules, such as the intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM), which is suppressed by treatment with insulin. Another example is the impairment induced by hyperglycemia in the function of neutrophils, including chemotaxis, phagocytosis, and respiratory function, which is attenuated with insulin [101].

13. Conclusions

As we observed, the epidemiology of IE has changed over time. *S. aureus* is currently the most important pathological agent as a cause of IE [4, 102]. The age group with greater participation is the older adult due to their comorbidities, especially cardiac ones, with the need for valve prosthesis placement, and vascular approach for the placement of cardiac pacemakers.

The existence of an immunogenetic influence in the risk and outcomes of infectious diseases has been well stablished. In the cases of IE and sepsis, investigation is ongoing to clearly define the specific genetic anomalies that contribute to this influence. The study of SNPs has been a good start in the understanding of the phenomena; nevertheless at the light of the information derived from their study, they do not seem sufficient to explain the whole participation of genetics in the sepsis and IE equation. Other types of genetic abnormalities might also participate, and it might be worth exploring [103]. Even though there is a large body of studies with positive results, there are also lots of contradictory and conflicting findings that make it difficult to make definitive conclusions. Even more, according to a systematic review made to determine the methodological quality of SNP association studies with sepsis, most of the studies could improve a lot methodologically speaking in terms of control group selection, genetic assay technique, study blinding, statistical interpretation, study replication, study size, and power.

Finally, the sequence of events that begin with an infectious state, such as IE, alerts and promotes inflammation through the immune system, both cellular and humoral to eliminate the infectious agent; however, this has the ability to evade the immune system.

In its evolution, the germ also generated the possibility of survival through the acquisition of resistance to external agents, such as antibiotics, which can perpetuate the septic process, increasing the production of reactive O_2 species both locally (cell-mitochondria) and systemic level (neutrophil-monocytes-macrophage-endothelium) together with the products that generate the interaction infectious agent-immune system.

The activity of antioxidant enzymes is exceeded, so that ROS cannot be eliminated, generating a state of oxidative stress, with a profound effect on the mitochondrial level by breaking the chain of electron transport, and, consequently, the genesis of the energy is compromised.

The repercussion of this sequence of events, both at the cardiac level and at the systemic level, is manifested by the failure of one or several organs.

In a schematic way, the sequence of events of a patient with IE who has a severe evolution and finally dies of multiple organ failure is shown (**Figure 3**).

Different studies explore areas of compromise such as metabolome and proteome in which it is observed that glycolysis, gluconeogenesis, and fatty acid

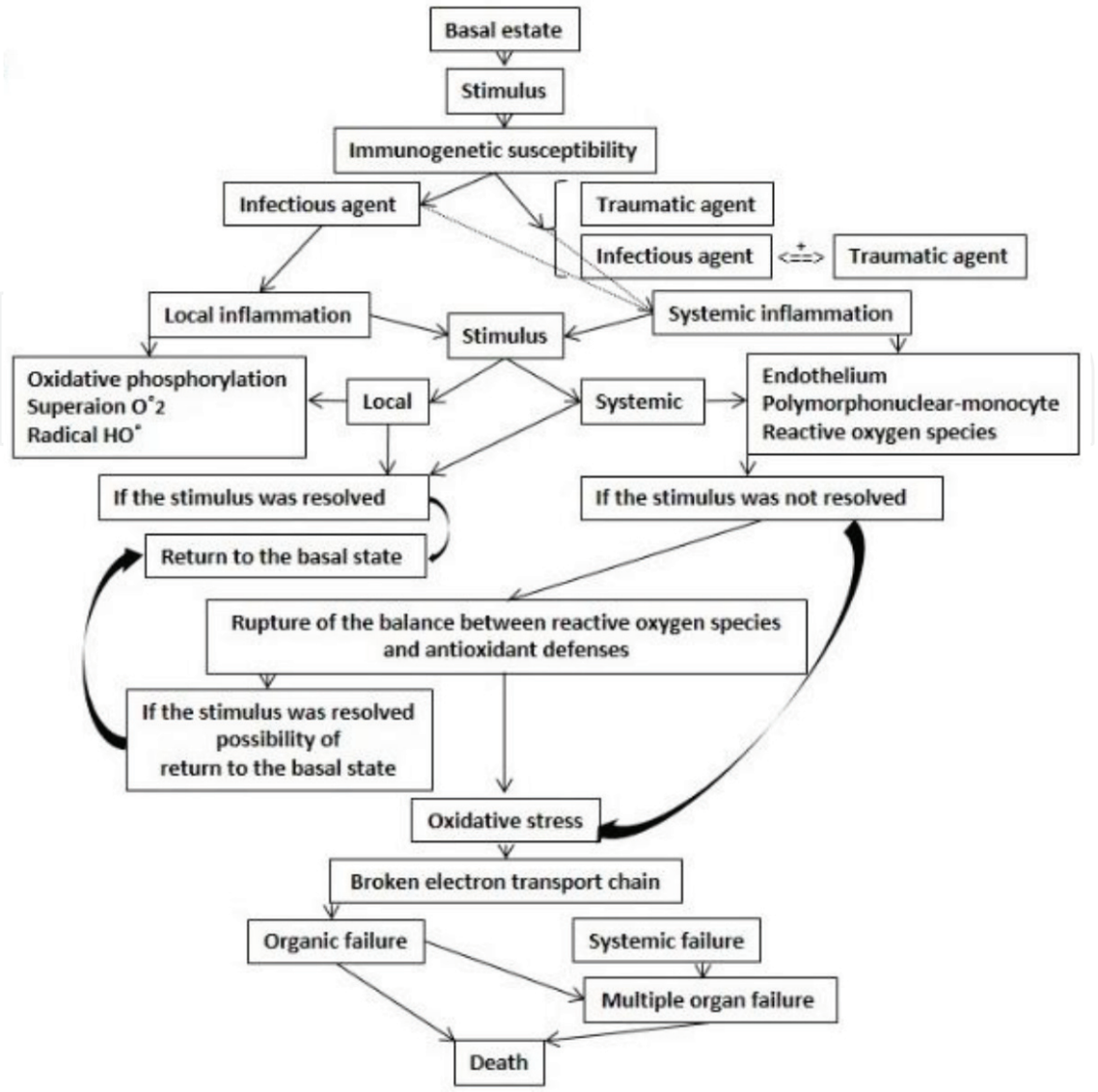

Figure 3.
Schematic representation of the sequence of events of a patient with IE who has a severe evolution and finally dies of multiple organ failure.

transport are damaged, so the substrate is low and the few substrates are not used by the mitochondria, which generates attention in processes to be repaired.

In another (acetylome) the possibility of normalizing the NAD + redox balance is observed both genetically and pharmacologically in the treatment of heart failure [91].

The observations of the behavior of cytochrome c, being a mobile complex molecule and crossing cell membranes, made it possible for cytochrome c to enter into cardiomyocytes to improve mitochondrial respiration, improving the survival of septic mice [92–94]. This open a very attractive opportunity in the treatment of septic patients with heart failure as in IE when in the future we use complex molecules, i.v., in the treatment of these patients.

There are still many areas in which it is necessary to continue researching in the clinical area as well as in the bacteriological, biochemical, and biomolecular areas in addition to other types of tools to observe systemic inflammation, through mathematical modulation and systems-based models of inflammation [104, 105], and the severity of a septic patient due to the complexity of losing the cardiac bioelectrical signal and how it recovers the complexity if the patient survives the septic event have also been considered [106].

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Conflict of interest

None.

Acronyms and abbreviations

MRSA	methicillin-resistant *Staphylococcus aureus*
HssRS	hem sensor system
hrtAB	hem regulator transporter
bNOS	nitric oxide synthase hemoprotein
TNF	tumor necrosis factor alpha
IL	interleukin
HMGB1	high-mobility group box 1 protein
GRO alpha	growth-regulated oncogene
RANTES	regulated upon activation, normal T-cell expressed, and secreted
EE	endocardial endothelium
Et-1	endothelin-1
ON	nitric oxide
PG	prostaglandins
VEGF	vascular endothelial growth factor
SNP	single-nucleotide polymorphism
GWAS	genome-wide association studies
LPS	lipopolysaccharides
A	adenosine
G	guanine
PBMC	peripheral blood mononuclear cells
IL-RNa*	The interleukin 1receptor antagonist gene
APACHE II score	acute physiology and chronic health evaluation
SIRS	systemic inflammatory response syndrome
ICU	intensive care unit
TLR	toll-like receptor
MyD88	adaptor-like protein
FER gene	tyrosine-protein kinase
TREMs	triggering receptor expressed on myeloid cells
ADP	adenosine diphosphate
NADH	nicotinamide adenine dinucleotide phosphate
FADH	flavin adenine dinucleotide
ROS	reactive oxygen species
IMM	inner mitochondrial membrane
OH•	hydroxyl
$RO•_2$	peroxyl
RO•	alkoxyl

HOCl	hypochlorous acid
O_3	ozone
$^1/_2O_2$	singlet oxygen
H_2O_2	hydrogen peroxide
RNS	reactive nitrogen species
SOD	superoxide dismutases
$2O^{\bullet}_2$	superoxide free radical
CuZnSOD	copper, zinc-superoxide dismutase
mtDNA	mitochondrial DNA
tRNAs	transfer RNAs
rRNAs	ribosomal RNAs
NOX	NADPH oxidase generically called
phox	adapter protein p22
TBARS	reactive substances thiobarbituric acid
iNOS	inducible nitric oxide synthase
NO	nitric oxide
JNK-AP1	Jak2-IRF1 pathway genes (*IFNGR1, IFNGR2, JAK1, JAK2, STAT1, IRF1*)
MOF	multiple organ failure
MODS	multi-organ dysfunction syndrome
CLP	cecal ligation and puncture
ICAM	intercellular adhesion molecule
VCAM	vascular cell adhesion molecule

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