

Molecular Markers in Diagnosis and Prognosis of Sepsis, Severe Sepsis and Septic Shock

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ABSTRACT

Background: Despite important advances in understanding the pathophysiology of sepsis, the mortality it generates remains high.

Objective: Describe the state of the art of molecular biomarkers proposed so far as potential markers for the diagnosis and prognosis of sepsis, severe sepsis and septic shock.

Results: The search yielded 3,370 references covering more than 30 genes with genetic polymorphisms that can be used as potential polymorphism markers. These were evaluated for its use in the different manifestations of sepsis, its diagnosis and progression. Twenty marker genes are described: four associated with bacteremia (TLR-1, TLR-2, Protein C and Selectin-E), nine with sepsis (IL-1B, IL-1A, IL-6, TNF- α , TLR-1, MBL-1, Hsp70, PAI-1 and MIF-1), seven with severe sepsis (IL-1RN, IL-10, TNF- α , CD14, TREM1, Caspasa 12 and DEFB-1), five with shock septic (TNF-B, TLR-4, Hsp70, MBL-1 and CD14) and three with dysfunction multi-organ (TLR-1, PAI-1 and

Protein C).

Conclusion: Genetic polymorphisms, for the most part, have been clinically proven as diagnostic markers and prognosis in sepsis with promising results due to discharge specificity and sensitivity in clinical practice.

Keywords: Sepsis; Biomarkers; Genetic polymorphism; Simple nucleotide polymorphism; Mini-satellite repeats (DeCS).

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INTRODUCTION

Sepsis, either severe, in septic shock or dysfunction syndrome multiorgan, currently constitutes the first cause of mortality in patients admitted to care units intensive (ICU), causing more than 60% of deaths in this service (1-4). In Colombia, the prevalence of patients with sepsis in the ICU it is 12% and the mortality rate reaches 33.6% (4). In the USA In the USA, the incidence of severe postoperative sepsis has tripled, going from 0.3% for the year 2000 to 0.9% in 2010 (2). In Europe, around 29% mortality is reported in patients who developed sepsis and severe sepsis (1,3). Sepsis does not present specific clinical manifestations and Its evaluation has limitations when establishing the severity and the predict disease prognosis effectively. In the topicality, the indicators used to monitor the clinic of infection include: fever, white blood cell count (WBC), determination of C reactive protein (PCR) and pro-calcitonin (PCT), among other parameters (5,6). The search for new biomarkers of high sensitivity and specificity that help improve the diagnosis and prognosis of sepsis is a field of study in molecular medicine (7). A approach to this type of research is based on establishing as a biomarker to variation in plasma concentration of proteins involved in the inflammatory response during illness (7-10). However, the polymorphism of the genes encoded by these proteins as a more reliable biomarker (11,12). This article reviews the state of the art of the Molecular biomarkers proposed so far as potential markers for the diagnosis and prognosis of sepsis, severe sepsis and septic shock.

MATERIALS & METHODS

The records of the last 14 years that were found were analyzed. Sorting items per year of publication and including only research articles and documents that evaluate or treat the keywords: sepsis, genetic polymorphisms,

genetic variation and molecular marker. They only had Take into account the articles published during the last 10 years.

RESULTS & DISCUSSION

The search yielded 3,370 references covering the generalities of the sepsis biomarkers, the theoretical bases of genetic polymorphism and the publication of more than 30 genes with polymorphisms considered markers of this disease. However, the review had into account 84 articles that described the epidemiological aspects and the theoretical bases of sepsis; as well as the biomarkers that include the polymorphism in 17 candidate genes, considered as potential molecular susceptibility markers for the development of sepsis, septic shock and mortality. Molecular biomarkers in sepsis Variation in plasma levels of generated molecules by effector cells during the inflammatory response to sepsis includes: reactive oxygen species (ROS), nitrogen metabolites (RNS), cytokines, chemokines, and increased receptor expression Of surface. These have been considered molecular biomarkers very useful to confirm or rule out the disease, as well as to evaluate the evolution of the patient in a specific therapy (7-10). Among the mediators, cytokines whose secretion stand out it is detected from the first moments of infection (11,12). So the high serum levels of IL-1 β interleukins, IL-4 IL-6, IL-8, the macrophage inflammatory protein (MCP-1) and osteopontin (OP) are considered indicators of poor prognosis of sepsis (13-17). Table 1 describes possible biomarkers identified in the bibliographic search. IL-1 β has been shown in animal models to be capable of inducing several of the symptoms of septic shock and dysfunction multiorgan (10,13), while interleukins IL-2, IL-6, IL-10, IL-12, IL-13, IL-18 and tumor necrosis factor (TNF- α) participate in the pathogenesis of severe sepsis (14-17). TNF- β (also called alpha lymphotoxin) is a cytokine that It has effects similar to those described for TNF- α , although it

has been found that the level of this cytokine in the serum of patients who developed sepsis is significantly higher compared to that of patients who did not develop it during an infectious process. Without However, its role in the pathogenesis of sepsis is unclear (10,14). IL-1 β , OP and MCP-1 are found in high plasma levels in septic patients (7-9) and the increase of IL-2 and IL-4 is related with the severity and development of sepsis (14). The high plasma level IL-6, IL-10, IL-12, IL-13, IL-18, MCP-1 and TNF- α is considered a predictor of fatal disease development (10,11,16,17). High mobility protein B1 (HMGB1) induces the activation of macrophages and monocytes and triggers cytokine release pro-inflammatory and regulation of adhesion molecules. This protein it occurs at high levels in patients with sepsis (18); However, It has a slower reactivity than TNF and IL-1 β , so it is dismissed as a biomarker to predict disease (19). In studies conducted on the function of markers cell surface, proteins from the cluster of differentiation (CD). Serum determination of CD48 proteins and high-level CD69 is related to the development of sepsis and low levels of CD10 and CD11 with a poor prognosis of disease (20). Similarly, high plasma levels CD14, CD18, CD25, CD28, CD40 and CD80 in patients with severe sepsis are reported as an indicator of poor prognosis of disease and lead to fatal cases (21-24). Other molecules of interest that are analyzed as biomarkers sepsis are pattern recognition receptors (PRRs) that recognize pathogen molecules (PAMP) and are part of the innate immunity (25). Among these, the receptor family stands out Toll-like (TLR), with at least 10 proteins recognized in humans; this family is expressed in macrophages, dendritic cells, neutrophils and in other cell populations and plays a role central in the innate immune response to infection by recognition of different bacterial antigens (26). For example, TLR4 identifies the lipopolysaccharide (LPS) of Gram bacteria negative, whereas TLR2 is essential in the recognition of Another marker is the soluble receptor for myeloid cells (sTREM-1) that is part of the receptor superfamily of immunoglobulins. In the studies by Arts et al. (27), it is proposed as a predictive biomarker of the development of severe sepsis. High serum levels of the

soluble IL-1 receptor are detected in septic patients, whereas soluble receptors of IL-2 α and TNF- β Linked to Shock Development septic and multi-organ dysfunction (13,14). Inflammatory molecules that act on the endothelium they have also been studied as biomarkers. In this case, the adrenomedullin peptide (ADM), regulated by the supplement, acts as a powerful vasodilator with effects bactericidal and has been pointed out by some studies as a good predictor of the severity and evolution of sepsis, according to the variation of their plasma levels in septic patients (28,29). Studies also point to leukocyte adhesion molecule of the endothelium (ELAM-1) and the growth factor derived from platelets (PGDF) with a fatal development of the disease (7,8,14). Selectins (surface proteins expressed by cells endothelial and that facilitate the leukocyte bearing) have been related to the development of sepsis, especially selectin S, the which has been proposed as a predictor of multi-organ dysfunction (7,8). In recent years, microRNA molecules have been studied (miRNA) as potential sepsis markers. It's about a peptidoglycan from Gram positive bacteria (25,26). The increase in serum levels of TLR2 and TLR4 it is detected in patients with sepsis and is related to the poor prognosis of the disease (26). type of small non-coding endogenous RNAs with about 22 nucleotides in length that participate in important functions biological by inhibiting the expression of messenger RNA (mRNA) (30). MiRNAs are involved in development and specific function of the tissues; Furthermore, due to their unique expression pattern, they are molecules considered as potential markers in diagnosis or as therapeutic targets for many diseases (30,31). The altered expression of this molecule is detected in the circulation of patients with sepsis, so its usefulness has been suggested as biomarker for disease diagnosis and prognosis (31). Despite the important role of miRNAs in the pathogenesis of sepsis, these represent limited value as biomarkers since its expression is also induced in other diseases not infectious. So you need to focus on other markers more specific. According to this approach, the studies are focus on studying genetic polymorphisms as markers molecules of sepsis.

Table 1: Possible humoral markers in sepsis.

Cytokine	Location chromosomal	Cell origin	Function	Possible partition in the pathophysiology of sepsis
Pro-inflammatory				
IL-1 β	2q14.1	Macrophages, monocytes	Cell proliferation, differentiation, apoptosis	High expression in septic patients vs. non-septic patients
IL-6	7p15.3	T lymphocytes, macrophages, cells endothelial	Cell differentiation, cytokine production	Disease severity, mortality
IL-8	4q13.3	Macrophages, epithelial cells, endothelial cells	Chemotaxis, angiogenesis	Greater expression in septic neutropenic patients vs. febrile neutropenic patients without sepsis
IL-12	3q25.33	B lymphocytes, Dendritic cells, macrophages,	IFN- γ production, TNF- α production, Th1 differentiation	Mortality predictor from postoperative sepsis. Used in the diagnosis of sepsis in pediatric patients

IL-18	11q23.1	Macrophages, monocytes, cells dendritic	Antimicrobial IFN- γ production, immunity	Useful to distinguish between Gram positive and Gram sepsis negative. Increased expression in trauma and sepsis patients vs. trauma-only patients
TNF- α	6p21.33	Macrophages, CD4 T lymphocytes, NK lymphocytes	Cytokine production, anti-infection, tumor necrosis	Useful to distinguish between patients with septic shock survivors and non-survivors 28 days after disease
Anti-inflammatory				
IL-1Ra	2q14.1	Macrophages, monocytes, cells dendritic	IL-1 α and IL-1 β inhibitor	Useful for early diagnosis of sepsis before symptoms in newly born
IL-4	5q31.1	T lymphocytes, mast cells, basophils	Cell proliferation, Th2 differentiation	Increases its levels associated with the development of sepsis
IL-10	1q32.1	Th2 cells, B lymphocytes, Monocytes	Cytokine production inhibitor Pro-inflammatory	increased expression in septic shock vs. cardiogenic shock
IL-13	5q31.1	Th2 cells	Cytokine production inhibitor Pro-inflammatory	Increase your levels in septic shock in sepsis
TGF- β	19q13.2	Macrophages, B lymphocytes	Inhibition of the production of pro- cytokines inflammatory	Disease progression

IL: Interleukin; TGF: tumor growth factor.

Genetic polymorphism

Genetic polymorphism corresponds to the change in the sequence of a gene and occurs more often than 1% in the population. Polymorphisms can occur in coding regions and not encoding the genome (32). There are two classes of polymorphisms genetic: the one generated by the replacement of a nucleotide and originates from the insertion or deletion of one or more nucleotides, single nucleotide polymorphism (SNP), and that which occurs when in a group a nucleotide is repeated in blocks, variable number tandem repeat (VNTR) (30,31). One way to classify SNPs is based on the effect they cause in protein function; in this way there are the linked (SNP indicative), which are variations that occur in untranslated regions to proteins and that do not affect the function of these. However, they can affect the susceptibility of contracting a certain disease (32). For example, SNPs in the promoter regions of a gene can alter the affinity of transcription factor binding and affect the concentration of the protein, while the SNPs generated at the terminal ends of the mRNA that are not translated can alter the stability of the latter and, consequently, the protein synthesis (32). Causative SNPs are those that directly affect function of the protein, cause disease, occur in the region encoding a gene and can change the amino acid sequence of the protein product with the probability that it affects its structure and

function. This type of SNP is a candidate for use as an allele. disease modifier (32.33). In the case of VNTRs, those that are detected in the coding region they can generate non-functional proteins, whereas if they are found in non-coding regions, alteration can result in brittleness chromosome, gene silencing and modulation in processes of transcription and translation (32-34). It has been argued that the presence of some of these polymorphisms genetic would be related to

the susceptibility of the individual to the development of certain diseases (34-37). For example, nucleotide variations in the PARK-2 or PACRG genes are related with the progression of leprosy (38). Some specific mutations in the gene that codes for TLR seem to be related to the development of tuberculosis (39). Mutations in genes α -globin, β -globin, SLC4A1, mal / tirAP and darC are related to susceptibility to malaria (40). Specific nucleotide variations have also been detected by the proteins that participate in the inflammatory response during infection in the genes they encode. Such variations are related with susceptibility to the development of sepsis and progression of disease (12,41,42). Genetic polymorphisms as biomarkers of sepsis Various studies link the genetic polymorphism of more than 30 genes with the development of sepsis, severe sepsis and septic shock. for pro-inflammatory cytokines, cell receptors, enzymes, chemical mediators, among others (41.42). Polymorphisms studied in cytokines Cytokines are considered physiological messengers of the response immune, they are active in low concentrations and bind to receptors specific in different cells, causing the release of secondary and other cytokine mediators, as well as the expression of multiple molecules that allow the activation of different cell populations (6-9.43). Various studies have related the presence of certain polymorphisms in the genes that encode them with susceptibility to infections, the different clinical forms of sepsis and mortality (44-57).

IL-1

IL-1 are potent proinflammatory cytokines released by macrophages involved in the systemic inflammatory response. This family is made up of two agonists (IL-1 α and IL1 β) and by an antagonist (IL-1 receptor antagonist: IL1ra) (6). The IL-1A, IL-1B, and IL-1RN genes encode IL-1 α , IL1 β

and IL-1ra, respectively, and are located in the genes that code for human leukocyte antigens (HLA) in area q13-21 chromosome 2 (6). Five have been identified polymorphisms related to the risk of developing sepsis: a SNP at position -889 of the promoter region of the L-1A gene, two SNP at position -31C and -511 of the promoter region and a SNP at position +3954 of exon 5 of the IL-1B gene (44,45). In the IL-1RN gene, a polymorphic region has been detected in the intron 2 with an 86 bp VNTR originating five alleles (A1, A2, A3, A4 and A5), which are prognostic markers to develop severe sepsis (46). The study by Fang et al. (47) found that 54% of healthy individuals present four copies of the 86 bp repeated (allele A4) and 34% two copies (allele 2). The allele 2 is associated with high serum levels of IL-1ra in numerous diseases where inflammation plays a central role. Some studies analyzed establish the association between polymorphism in IL-1 with the development of sepsis; However, the The results of these are inconsistent and inconclusive (43,44). By their part, Zhang et al. (45) performed a meta-analysis with the literature published related to polymorphism in the IL-1 gene as risk factor for the development of sepsis in the databases of PubMed and Embase and on the web until June 2013; these authors they also found that for the SNP at -889 IL-1A (rs1800587) a significant association (OR = 1.47; 95% CI: 1.01-2.13; p = 0.04), while with the -511 IL-1B (rs16944) or -31 polymorphisms IL-1B (rs1143627) no association was evidenced. In the case of the SNP+3594 IL-1B (rs143634), the TT genotype represented a lower risk of suffer the disease (OR = 0.59; 95% CI: 0.36-0.97; p = 0.04). An association was found for the VNTR in the IL-1RN gene significant with the development of sepsis (OR = 1.40; 95% CI: 1,011.95; p = 0.04); further, the increase of the VNTR was related with an increased risk in the severity of the disease (45).

IL-6

IL-6 is a pleiotropic cytokine secreted by several cells, among which stand out macrophages, fibroblasts, endothelial cells and T cells (6). The gene that codes for IL-6 is located in the chromosome 7, generated by the change from G to C in position -174 G / C of the promoter region, and is related to a lower sepsis mortality when patients have the GG genotype (48). SNPs at position + 1753C / G have also been identified and +2954 G / C, which has not been conclusively demonstrated its relationship with the risk of developing sepsis (7). In a study conducted with surgical patients, mortality in sepsis was significantly lower in homozygous subjects GG (OR = 0.11; 95% CI: 0.02-0.57). In this same investigation, patients who died had serum IL-6 levels, that is say significantly higher compared to those of those surviving patients (GG genotype) (49). This results were consistent with those obtained in a study carried out in a German hospital, in which patients carrying the genotype homozygous GG were associated with improved survival in sepsis significantly (50). A SNP has also been found at position +5174 in the promoter region of this gene and a positive association with neonatal sepsis (51). However, a larger number of studies are needed to confirm these results.

IL-10

IL-10 is the most potent anti-inflammatory cytokine that regulates the decrease of proinflammatory cytokines and chemokines secreted by monocytes, neutrophils, and eosinophils; prevents activation of T cells; It inhibits the expansion of T cells, and enhances the release of the IL-1ra inflammatory modulator (6). The IL-10 gene is located on chromosome 1, at position 1q31-1q32 (20). Three SNPs have been determined in the region of this gene: -1082A / G, -819C / T and -592C / A (52-55). The A allele is related to the -1082A / G polymorphism and is associated with susceptibility to the development of sepsis (52); In contrast, the -1082G / G genotype has been associated with lower mortality (53,54), while in the G allele (-819T / G) it was observed that patients present higher levels of IL-10, with a notable increase in mortality caused by severe sepsis (54). The allele generated by the SNP in -592A is associated with low levels of IL-10 and an increased risk of mortality as a consequence of the sepsis (55,56). Shu et al. (57) carried out a study in China to investigate SNPs at positions -592, -819 and -1082 and found that these were associated with a higher incidence of severe sepsis. Patients with severe sepsis were more likely to have allele A (-1082A) and those who survived it presented lower levels of IL-10 and higher frequency of the G allele (-1082G), compared to controls (17% vs. 47.2%; p = 0.012). In Regarding the allelic forms of SNP -592 and -819, it was not found association with mortality risk (57).

TNF

TNF- α is a secreted multifunctional proinflammatory cytokine predominantly monocyte / macrophage and T cells (6). TNF- β , also called lymphotocin α (LT- α), is a cytokine produced by T lymphocytes that activates endothelial cells and neutrophils and acts as a mediator of the inflammatory response acute and T cell activation. The genes encoding the TNF- α and TNF- β proteins are located within the human leukocyte antigen (HLA) class III genes, on chromosome 6 position 6p21.3 (6). Paper of the polymorphisms of these genes with susceptibility to sepsis has been evaluated in different populations around the world (7,8). Several SNPs have also been reported in the promoter region of the gene that codes for TNF- α and some have been related to the development of sepsis. The most studied polymorphisms are found at the -308 site that generates the G / A nucleotide change (58,59). The resulting alleles of SNP -308 G / A are named TNF1 and TNF2; G-containing copies correspond to the TNF1 allele and those containing A correspond to the TNF2 allele (58). The highest plasma levels of TNF- α are detected in patients who died with a T / A-308 SNP and were more susceptible to developing severe sepsis. and septic shock (59). A second polymorphism was detected at position -238G / A at the junction with the repressor, located in the promoter region where the allele A replaces the more common allele G and is associated with low levels of gene expression (60). The 250 G / A variation is associated with a high level of mortality in septic shock in adults and bacteremia in children (61). Dwyer et al. (62) examined the association of polymorphisms in the promoter region of the TNF- α gene and mRNA levels in a cohort of

patients with severe sepsis and found that in the homozygous patients had higher mRNA production for the allele G (SNP at position -308) than those carrying the A allele (SNP at position -863). Patients carrying haplotype 1 (allele A and G) also presented a higher level of mRNA, while the haplotype 4 carriers (with C in position -863 and A in position -308) presented decrease in mRNA levels. The patients homozygotes for allele A at position -308 presented higher mortality in severe sepsis than carriers of the G allele. In the case of the gene that codes for TNF- β , a SNP G / A in the +252 region located on an intron. The allelic variant with G it is called TNFB1 and is related to a higher TNF- β production, while the variant with A is called TNFB2 and is related to increased production of TNF- α (43). Studies conducted on Caucasian Germans with shock septic have shown that patients with the TNFB2 allele have a greater secretory capacity of TNF- α with respect to the TNFB1 allele and that the TNFB2 allele is also associated with an increased risk of death. Among postoperative patients with severe sepsis, the 65% of those who did not survive were homozygous for the allele variant (TNFB2 / B2) (9). However, a study conducted in Brazil with 60 sepsis patients and 148 healthy blood donors established the relationship of the TNFB2 allele with susceptibility to sepsis, but this was not found to be associated with immunological and clinical biomarkers of the disease (63). Polymorphisms in cellular receptors TLR There are studies that have tried to quantify the effects on genetic variation in TLR during the inflammatory response to PAMP and the risk of organ dysfunction or death in patients with sepsis. Wurfel et al. (64) conducted a cohort study in sepsis patients analyzing the TLR-1 polymorphism in position -7202A / G (rs5743551) and they found that the G allele was related to the high production of cytokines. This SNP is generated in the coding region of the gene and causes increased gene induction by the activation of NF- κ B. Consequently, LTR1 is expressed to a greater extent on the surface of the cell (64). The patients with sepsis that presented the G allele they had an increased risk of multi-organ dysfunction and death (OR = 1.82; 95% CI: 1.7-3.9). In this same investigation, a case-control study was carried out and it was found that the G allele was associated with the risk of suffering sepsis-related acute lung injury (OR = 3.40; 95% CI: 1.59-7.27). Furthermore, this allele was found in a higher proportion in patients with sepsis due to Gram positive bacteria. The TLR-2 polymorphism at position -16.933A, causing the exchange of arginine for glycine at position 753 of the receptor (Arg753Gln), is related to bacteremia caused by bacteria Gram positive with development of sepsis and septic shock (65). The SNP at position + 896G of the gene encoding the TLR-4 results in a substitution of glycine for aspartic acid at position 299 of the amino acid sequence (Asp299Gly) and it is associated with higher mortality in patients with syndrome of systemic inflammatory response (SIRS) and with the development of sepsis in patients with trauma or burns (66). The other SNP results in a change from threonine to isoleucine at position 399 of the amino acid sequence (Thr399Ile), this SNP triggers a higher prevalence of infections by Gram negative bacteria (67). The Asp299Gly and Ile399Thr variants reduce the levels of IL-1 α

and the response to lipopolysaccharide endotoxin (LPS) in infected patients. The study by Schröder & Schumann (68) identified an association positive between Thr399Ile polymorphism and premature births. However, as the allele frequency of this polymorphism TLR4 is low (6-10%), more studies are necessary epidemiological to verify it.

CD14

The CD14 molecule is a 53 KDa receptor glycoprotein that is expressed on the surface of monocytic cells. In addition to this cell form, there is the soluble form (CD14s), which induces the cascade inflammatory when bound to the LPS of Gram negative bacteria (6). The gene encoding the CD14 molecule has a SNP in the promoter region at -159T / C and set as a marker predictive of mortality and severe sepsis in burned patients (65). The T allele was found related to an increase in septic shock and the TT genotype was a risk factor for mortality (OR = 5.3) (69).

TREM-1

The TREM protein is part of the immunoglobulin superfamily that are expressed in polymorphonuclear granulocytes and monocytes ripe. Its expression is induced by infection by bacteria and fungi (7-9). The VNTR rs2234237, detected in the gene that codes for TREM-1 protein, is associated with mortality in septic patients; the VNTRs rs7768162 and rs9471535 of the TREM-1 gene are related with severe sepsis and rs2234237 is associated with high mortality at 28 days in patients with sepsis (70). It then arises that TREM-1 can be used as an ideal biomarker of fatality for the diagnosis and prognosis of sepsis. Genetic polymorphisms in molecular effectors of the inflammation Mannose Binding Lectin (MBL) MBL is a lectin that recognizes polysaccharide motifs of various pathogens and its main function is to participate in the opsonization (6). SNPs in position -221C and -550C in the promoter region of the gene encoding MBL are related to low levels of the protein in patients who developed sepsis and septic shock (71). Polymorphisms have also been identified in the region coding gene that generate three amino acid changes in positions 52TGT, 54GAC, and 57GAA of the MBL protein (are called variants D, C and B, respectively), which causes instability in protein folding and development of pyelonephritis, bacteremia, and septic shock from infection by *Escherichia coli* (72).

HSP70

The Hsp70 protein family acts as a mediator inhibitor inflammatory produced by the nuclear factor activation pathway kappa, beta (NF- κ B). It is encoded by three genes (HSPA1B, HSPA1A, and HASA1L) located in the HLA region in chromosome 6, close to the region coding for proteins TNF- α and complement (6). Polymorphisms have been detected in the coding region of the HSPA1B gene at position +1267 (allele A) and position -179 (allele C). The -179C / +1267A haplotype is related to production significant of HSPA1B and TNF- α in response to exposure to Gram negative bacteria (73). Sapru et al. (74) showed that patients with the AA genotype at position +1267 presented higher risk of developing septic shock than those who they

presented the G allele, either homozygous or heterozygous. Human β -defensin 1 (DEFB1) DEFB1 is a peptide with microbicidal and cytotoxic activity, secreted by neutrophils and multifunctional mediator in infection and inflammation. This peptide has been extensively explored in the ex vivo studies (6). In the DEFB1 gene, a SNP is detected at position -44G that generates severe sepsis and increased mortality from this disease (75). Fang et al. (76) investigated variations in the gene associated with development of sepsis and found six polymorphisms: the genotype with the -44G / -44G alleles were significantly associated with the incidence of severe sepsis; the -20G allele and the GG genotype were related to susceptibility to severe sepsis, while the genotype with the alleles -1816G / -1816G-allele influenced the outcome of severe sepsis; the -20A / -44C / -52G haplotypes showed a protective role against severe sepsis, and the -20G / -44G / -52G haplotype was a risk factor for the fatal development of severe sepsis. Plasminogen activator inhibitor type 1 (PAI-1) It is a 50 kilodalton glycoprotein that belongs to the family of serine protease inhibitors that promote coagulation; the PAI-1 acts as an acute phase protein during inflammation and its levels are related to increased severity of patients with sepsis (6,7,10). In the gene that codes for this protein have been found nucleotide variations in its promoter region; what produces the 4G / 4G genotype, which is associated with increased levels plasma PAI, development of sepsis, organ dysfunction and mortality (77). Binder et al. (78) showed that the predisposition genetics to produce high levels of PAI-1 (the 4G / 4G genotype) It is associated with a poor prognosis for severe sepsis. The 4G allele of PAI-1 is linked to high plasma concentrations of PAI-1 and to low patient survival, while polymorphism 4G / 5G is linked to the development of systemic meningococemia and disseminated intravascular coagulation (78). Macrophage migration inhibitory factor (MIF) This factor is produced by various cells and plays a role important in the pathogenesis of acute inflammatory diseases and chronic, as well as in autoimmune disorders (6). In patients with sepsis, high serum MIF levels have been detected and they correlate with the severity of the disease (7,8). The SNP detected at position -173C of the gene that codes for MIF is related to the development of sepsis in patients with pneumonia associated with the community, just like a detected repeated sequence at position -794 CATT, causing an increase in levels of protein (79).

Caspasa 12

Caspases are key enzymes in mediating events proteolytics in the cascades of inflammation and cell death by apoptosis. Caspase 12 (Csp-12) is found in this group, which is phylogenetically related to the maturing caspases of

cytokines (caspases 1, 4, and 5), known as inflammatory caspases (6). Saleh et al. (80) detected a SNP in exon 4 of the gene that codes for caspase 12 with a 125T> C change, which leads to the alteration of a stop codon by an arginine, which in turn originates the synthesis of a truncated protein (Csp-12S) or a longer protein (Csp-12L). This long form is related to development of severe sepsis. A study by Mejía et al. (81) in 81 patients from Medellín diagnosed with sepsis, 23 healthy individuals from a population African American from Chocó and 24 healthy individuals from Medellín sought to analyze the 125T> C polymorphism of Csp-12 and found that the allele L is more frequent in African-American individuals and, in a lower proportion, in the mestizos, which indicates that the African-American population from Colombia may be more susceptible to severe sepsis than mestizo populations. Genetic polymorphism in the coagulation system of the host Protein C Endogenous and plasma levels of protein C in patients with sepsis they are inversely associated with the evolution of the disease and mortality (6). The gene that codes for protein C is located in chromosome 2q13-14 and polymorphisms have been identified in the untranslated region 5' at positions -1654CT and -1641AG, both they affect transcription and are related to severity of sepsis (82). The CA haplotype in this SNP has been associated with an increased risk of organ dysfunction and death, whereas the CG haplotype is related more frequently in patients with meningococemia (83).

Selectin E

Selectin E is a surface protein that is expressed in endothelial cells and that mediates the rolling of leukocytes (6). Jilma et al. (84) investigated the effect of the Ser128Arg change from selectin E that is produced in inflammation and coagulation in human volunteers who received doses of LPS. The markers of coagulation were higher in individuals with the polymorphism compared to controls with the normal genotype. The change was associated with an increase in inflammation and clotting of patients infected with Gram negative bacteria. Table 2 summarizes the main SNPs determined as markers.

Genetic susceptibility to sepsis in populations

Due to SNPs and VNTRs, genetic polymorphism causes allelic and locus heterogeneity between populations. The combined action of these biomarkers determines the degree of response to sepsis, which varies from person to person. The final phenotype found in the patient may be the reflection of the SNPs that have been inherited together over thousands of years of evolution (haplotypes) and that have evolved by interacting with each other.

Table 2: Genetic and phenotypic clinical polymorphisms related to sepsis.

Gene	Region of the SNP	Alleles	Associated disease	Reference
Cytokines				
IL-1 β	Promoter	-31C/T	Severe sepsis in burns	Chen et al. (44)
	Promoter	-511C/T	Severe sepsis	Zhang et al. (45)

	Exon 5	3953 C/T	sepsis	Zhang et al. (45)
IL-1 α	Intron 2	VNTR 86 pb	Severe sepsis	Fang et al. (47)
	Exon 2	2018	sepsis	Zhang et al. (45)
IL-6	Promoter	174G/C	Neonatal sepsis	Chauhan et al.(49)
IL-10	Promoter	1082G/A	Neonatal sepsis	Kang et al. (54)
		819C/T	Neonatal sepsis	Quiang et al. (57)
		-592C/A	Neonatal sepsis	
	-592 C/C	sepsis	Quiang et al. (57)	
TNF- α	Promoter	-308G/A	Septic shock	O'keefe et al. (58)
			TNF1 allele with G and TNF2 allele with A	Teuffel et al (59)
	Promoter	-238G/A		Schueller et al.(60)
TNF- α	Promoter	250 G/A	Septic shock in adults and bacteremia in children	Odwyer et al.(62)
TNF- β	Intron 1	252G/A	Severe sepsis	Delongui et al. (63)
			TNFB1 allelic variant with G	Delongui et al. (63)
			TNFB2 allelic variant A	Delongui et al. (63)
Receptors				
TLR-1	Promoter	-720 A/G	multi-organ Sepsis, dysfunction syndrome	Wurfel et al. (64)
TLR-2	Exon	2258G/T	Positive Septic shock by Gram-	Shutterland etal.(65)
TLR-3	Exon	896G	Sepsis with trauma or burns in patients	Wang et al.(66)
CD14	Promoter	-1595C/T	Sepsis in Chinese population	Wang et al.(66)
	Promoter	-260C/T	Neonatal sepsis	Baier et al. (56)
	Promoter	-159C/T	Septic shock	Zhang et al. (69)
Other proteins				
Hsp70-2	Region coding	1267 G/A	Sepsis	Ramakrishna et al. (73)
Protein C	Promoter	-1654CT, -1641AG	Dysfunction syndrome multi-organ	Chen et al. (82)
TREM-1		Rs2234237 A/T	Severe sepsis	Jung et al. (70)
Caspase12	Exon	125 T/C	Severe sepsis	Saleh et al. (80)
DEFB1	Promoter	-44G C/T	Severe sepsis	Cheng et al. (75)
MBL	Promoter	-550C, -221G	Pyelonephritis, bacteremia and septic shock from E. coli	Gordon et al. (71); Smithson et al. (72)
PAI-1	Promoter	4G/4G	Dysfunction syndrome multi-organ	Biender et al. (78)
MIF	Promoter	-173 C/T	Sepsis associated with pneumonia	Tende et al.(79)
Selectina E		561 A/C	Inflammation and bacteremia	Jilma et al. (84)

SNPs or VNTRs have been associated with various populations such as Asian and European, as well as some countries in Africa and various places in America. Certain SNPs related to sepsis they can be accentuated in some populations that present a greater severity and mortality when the disease has manifested itself. By example, SNP -1641 A / T and 1654C / G in the IL-6 gene are related with an increase in IL-6 levels, development of sepsis and organic dysfunction in the Chinese population (85,86). A variant detected at position -572 with a change from C to G in the region promoter of this gene reduces its transcriptional activity and is associated with a low risk of developing sepsis, specifically in the group Han ethnic group from China (87). Chen et al. (75) and Chen et al. (88) found SNPs in genes Trem-1 and Defb1 in this group have a predisposition to develop severe sepsis. Polymorphisms in the regions were also studied. encoding the Itr4, cd14, TNF and IL-10 genes in the population Japanese (89) and a VNTR (rs2069912) in the gene that codes for C reactive protein in

indigenous populations of North America and East Asia with fatal development in severe sepsis (90). Variation has been found in African and American populations of the IL-6 gene at position -174 G / C and at position -260 C / T of the CD14 molecule as predictive markers of mortality in sepsis induced by prolonged mechanical ventilation (87). In the Caucasian populations the -376G / A allele gene has been identified. TNF- α that is related to an increased production of cytokine (91). In the case of SNP 125T / C, in the gene that codes for caspase 12 (protein involved in programmed cell death), the frequency of the L allele is much higher in African American populations, where this allele has been detected opening the possibility that this population could be more susceptible to developing severe sepsis (81). All these associations allow a deeper analysis when relating the genotype of a patient with disease susceptibility. Without However, it is necessary to evaluate all these markers in order to obtain a susceptibility pattern that allows defining

the markers with a high percentage in the development of sepsis.

CONCLUSION

Sepsis is a public health problem that must be intervened with timely strategies to decrease the mortality rate. The search for new biomarkers to assess the severity of disease and predicting patient prognosis is challenging important that it provides a new idea to deal with sepsis. The use of molecular biomarkers has its foundation in the fact that each patient has his own gene pool with different degree of response to diseases, so it constitutes an important role in determining susceptibility for the result of diseases as complex as sepsis.

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