

Pathophysiology of Sepsis in the Elderly: Clinical Impact and Therapeutic Considerations

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Abstract: The aging world population will increase the incidence and mortality of severe sepsis. The aim of the present article is to review the pathophysiological differences in sepsis and its clinical impact on the elderly. The impact of immunosenescence on innate and acquired immunity is associated with relative immunologic depression that may favor the spreading of inflammation. Elderly patients also have enhanced apoptotic pathways that may contribute to the incidence of mortality due to sepsis. The inflammation-coagulation network is activated by age, explaining the success of some specific therapies. The initial clinical picture of sepsis in the elderly may be ambiguous but the specific pathophysiological changes of aging increase the risk of a sudden deterioration to severe sepsis with the development of a serious cardiovascular dysfunction. The reduced stress tolerance characteristic of aged tissues explains the high incidence of multi-organ failure in such patients. The specific pathophysiological and clinical picture of sepsis underlies the increased mortality in such patients and prompts research on therapeutic strategies with particular benefits to elderly septic patients.

Key Words: Aging, sepsis, immunology, immunosenescence, apoptosis, coagulation, shock.

INTRODUCTION

The aging of the world's population is an interesting demographic trend with important consequences in many fields including social sciences and medicine. The process probably will go on in the coming future. Sepsis is a life-threatening immune response to an infection contributing to nearly 20% of all in-hospital deaths. The incidence of severe sepsis increases with age and septic patients have a mean age of around 65 years. The decline of immune function that accompanies aging is prominent among the many factors contributing to the enhanced susceptibility of elderly patients to sepsis. Elderly persons are usually considered those over 65 years old. Anyway persons between 65 and 85 years of age are defined as "young elderly" because they usually differ from people younger than 65 years of age more regarding psychological and social factors than physiological ones. People older than 85 years of age are considered as "old elderly" and they show all the physiological features typical of aging. The epidemiology and clinical picture of sepsis in the elderly has been recently reviewed [2].

The aim of this article is to review the pathogenetic differences of sepsis in the elderly that can increase its incidence and mortality, with emphasis on the immunologic changes, clinical impact and possible new therapeutic strategies.

PATHOPHYSIOLOGY OF SEPSIS

Recent studies have elucidated the mechanisms underlying the septic syndrome, that derives from an immunologic

response to different insults (Fig. 1) [3,4]. Interesting insights into the first steps of innate immunity response have been recently elucidated [4,5]. Germ-line encoded receptors recognize highly conserved structures of many microorganisms that have been defined as pathogen-associated molecular patterns including lipopolysaccharide, peptidoglycan, lipoteichoic acids, mannans, bacterial DNA, double stranded RNA and glucans [5]. Soluble receptors for these molecules, like the mannan binding lectin, trigger the complement cascade [5]. Macrophages and dendritic cells have other receptors called pattern recognition receptors that have been classified as endocytic and signaling. Endocytic pattern recognition receptors mediate the phagocytosis of microorganisms and their delivery to lysosomes where their proteins are processed into peptides that can be presented by the major compatibility complex (MHC II) molecules on the surface of antigen-presenting cells. Signaling pattern recognition receptors include the toll like receptors (TLR) which activate signal transduction pathways through mitogen-activated protein kinases, determining the activation of nuclear factor NF- κ B and the transcription of many genes including those encoding for cytokines [4,5].

The first TLR studied in humans was TLR-4 that is implicated in the recognition of lipopolysaccharide (LPS). After the interaction of LPS with the serum LPS binding protein, this complex links CD14, a receptor on the surface of antigen presenting cells. The interaction with TLR-4 requires another surface protein, MD-2 [5]. The complex lipopolysaccharide-CD14-MD2-TLR4 induces the expression of cytokines, CD80 and CD86 in antigen presenting cells [5]. CD80 and CD86 are molecules of the cell surface necessary for the activation of T-cells. T-cells have an antigen receptor to recognize the peptides processed in the lysosomes and presented by MHC class II. Anyway the interaction between

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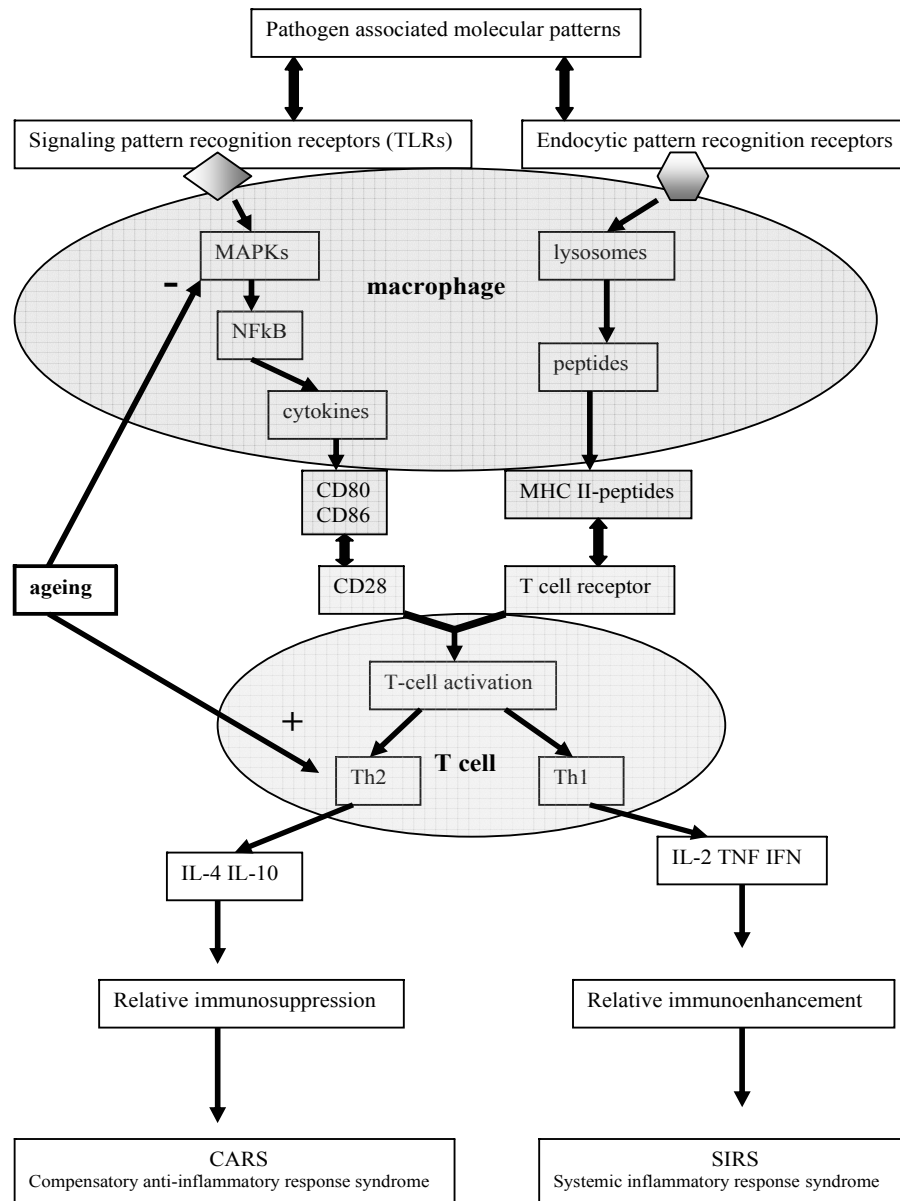


Fig. (1). Aging and pathophysiology of sepsis.

antigen receptor and the peptide-MHC complex is not sufficient to activate T cells, and could even lead to their permanent inactivation or apoptosis in the absence of another stimulus represented by CD80 or CD86. Recently ten TLRs have been identified in humans, each one can recognize specific pathogen-associated molecular patterns, but also some proteins derived from human themselves such as pancreatic elastase [6]. TLR-1 seems to be involved in the regulation of TLR-2 and TLR-4 signaling, TLR-2 responds to peptidoglycan (a wall component of Gram-positive bacteria), lipopeptides and lipoproteins [7]. TLR-3 interacts with viral double-stranded RNA [8], TLR-4 recognizes lipopolysaccharide of

Gram-negative bacteria and probably pancreatic elastase [9], TLR-5 responds to bacterial flagellin [10], TLR-9 recognizes specific bacterial DNA patterns containing CpG, while the role of TLR-6, 7, 8 and 10 remains unclear [11].

TLR activation, as previously stated, triggers the macrophage release of many proinflammatory mediators, including arachidonic acid derivatives (prostaglandins) and cytokines. TNF-alpha is the main mediator in the response to Gram-negative bacteria [2]. Almost every human cell has receptors for TNF-alpha. Low doses of this cytokine act locally, mainly on leukocytes and endothelial cells, increasing bacte-

rial killing and endothelial permeability. TNF-alpha also induces the release of IL-1 and IL-6 and the activation of the coagulation cascade through the production of factor VII. At higher doses, TNF-alpha may act on hypothalamic cells, inducing fever and on hepatocytes, causing the release of acute phase serum proteins. A further increase in TNF-alpha may result in myocardial depression and vasodilation [4,5]. Metabolic effects of TNF-alpha include the inhibition of lipoprotein lipase and the activation of gluconeogenesis. IL-1 is also produced by activated macrophages and endothelial cells [5], it acts on lymphocytes and endothelial cells with effects similar to TNF-alpha. IL-6 is produced by macrophages, endothelial cells and other cells in response to TNF-alpha and IL-1. IL-6 induces the synthesis of acute phase serum proteins, it is a growth factor for B-cells and a co-stimulator for T-cells [5]. IL-12 derives only from macrophages and B-lymphocytes. It activates natural killer cells, stimulates CD8+ lymphocytes and helps differentiate CD4+ T lymphocytes from T helper 1 lymphocytes [5].

When activated macrophages reach the lymph nodes they interact with lymphocytes, presenting them with the processed antigens and contributing to their appropriate stimulation as previously described. CD8+ lymphocytes are activated to become cytotoxic cells, CD4+ lymphocytes will differentiate into T helper 1 or 2 lymphocytes [4]. T helper 1 are immuno-modulating cells producing IL-2, TNF-alpha and interferons. IL-2 is a growth factor for T-cells. T helper 2 is implicated in allergic reactions and immunosuppressive mechanisms through the release of IL-4 and IL-10. This cytokine, that can also be produced by macrophages, inhibits the production of TNF, IL-1 and IL-12 from macrophages. Moreover, it decreases the expression of class II MHC and co-stimulatory molecules. IL-10 inhibits many functions on T-cells [4].

The septic syndrome is usually associated first with an intense stimulation of the immune system triggered by TNF, IL-1 and IL-2 and resulting in the systemic inflammatory response syndrome (SIRS). This is followed later by an inhibition of the immune system sustained by IL-10, the so called compensative antinflammatory response syndrome (CARS) [5]. When inflammation becomes systemic, the diffuse activation of neutrophils that adhere to the endothelial cells causes endothelial dysfunction and damage resulting in fibrin deposition, increased permeability, interstitial edema and reduced oxygen diffusion to tissues. Also, mitochondria of septic patients have impaired oxygen metabolism that results in cellular energy failure. If they are not stopped appropriately, all these alterations lead to multi-organ failure syndrome which includes the failure of the gastrointestinal tract, kidneys, cardiovascular system, central nervous system, hemopoietic system and liver. It is obviously associated with high mortality.

IMMUNOSENESCENCE

The immune system of the elderly is different from that of younger adult patients. All the components of the immune system appear to be somewhat altered in the elderly (Table 1). Innate immunity was previously considered to be well preserved in the elderly, but recent studies have pointed out significant alterations in these components [2]. The atrophy

of the thymus associated with age determines a shift from naive T cells to memory T cells that could be associated with a shift in the cytokine environment and an increase in cytokines characteristic of Th2 cells.

Table 1. Immunosenescence

Innate Immunity	↓ function of macrophages
	↓ expression of TLRs
	↓ function of mitogen-activated protein kinases
	↓ production of TNF-alpha and IL-6
	↑ production of IL-10
T-cells	↓ bactericidal activity
	↓ naive cells
	↑ memory cells CD45Ro+
	↓ function of mitogen-activated protein kinases
	↓ type 1 cytokine response (IL-2, TNF-alpha)
B-cells	↑ type 2 cytokine response (IL-4, IL-10)
	↓ number of B-cells and plasma cells
	↑ polyspecific immunoglobulins with low affinity produced by B1-cells
	↓ response to neoantigens

Innate Immunity

Elderly individuals have functional impairment of innate immunity, although many mechanisms related to this component of the immune system appear well maintained even at extreme ages [2]. Soluble elements of the innate immunity including complement mannose binding lectin and other antimicrobial peptides show retained activity [2]. On the contrary, cell elements of innate immunity show many functional impairments although they remain stable in number. The function of macrophages seems to undergo significant impairments with age. Ten years ago Nicholson *et al.* demonstrated that alveolar macrophages of aged mice are not efficient at presenting antigens to T cells [12]. In 2002 Renshaw *et al.* found that TLR expression in splenic macrophages was reduced in aged mice when compared with that in young ones [13]. They also observed that splenic macrophages from aged mice secreted significantly lower levels of IL-6 and TNF-alpha in response to LPS [13]. The overall reduction in TLR expression observed in aged mice was associated with important differences in the expression of specific TLRs, especially with a significant reduction in TLR-9 expression [13]. When a macrophage with TLR-9 activated by bacterial DNA containing CpG sequences presents antigens to T helper cells they switch to a Th1 response. Therefore the lower TLR-9 expression on aged macrophages could be associated with altered cytokine pattern production from T helper cells.

These studies suggest that the altered expression and function of TLRs due to aging affects not only the magnitude

but also the quality of the host immune response to pathogens by the altered inflammatory and priming environment [13]. These results were confirmed in 2004 by Boehmer *et al.*, showing that macrophages from aged mice are functionally impaired [14] showing a decreased proinflammatory cytokine production and endotoxin-stimulated activation of mitogen-activated kinases. These observations suggest that decreased mitogen-activated kinase expression could be a mechanism responsible for the impairment of TLR functions associated with aging.

Chelvarajan *et al.* recently found decreased production of proinflammatory cytokines and increased production of IL-10 by macrophages from aged mice. Immune response and signal transduction genes were specifically reduced in aged macrophages. Genes in the TLR-signaling pathway leading to nuclear factor-kappaB activation were also down-regulated in aged mice [15]. Boehmer *et al.* in 2005 found that non TLR signalling pathways are less impaired in aged animals, concluding that age-associated macrophage signalling alterations are specific for the TLR pathway which is impaired at the level of mitogen-activated protein kinase expression [16].

Another important function of macrophages is bactericidal activity due to stimulation with IFN- γ . This function is reduced in the elderly as well as nitric oxide and hydrogen peroxide generation [2].

Fulop *et al.* elucidated neutrophil function changes during aging, finding an alteration of the receptor-driven functions of human neutrophils, such as superoxide anion production, chemotaxis and apoptosis [18]. One of the alterations underlying these functional changes is a decrease in signalling elicited by specific receptors [18]. Plackett *et al.* confirmed these results, demonstrating defects in superoxide generation and increases in apoptosis in neutrophils from elderly patients after antigen stimulation [18]. Also the lytic activity of natural killer cells seems to be impaired although this kind of cell population expands with age [19]. Without this expansion, poor long term prognosis has been observed in elderly patients probably because of impaired recognition and destruction of infected cells [19].

Adaptive T-Cell Immunity

Immunosenescence affects significantly the adaptive immune response with important impairments in cell mediated immunity [2]. Aging is associated with a shift of the T-cell repertoire from naïve T-cells to memory T-cells [2]. This shift depends on the atrophy of the thymus that is essential to maturation of T cells, segregation into CD4+ and CD8+ cells and clonal specificity of the T-cell receptor [21]. These functions of the thymus decrease during adult life and by the age of 60 the organ has lost most of its activity [21], even if even in aged persons thymic T cell maturation by CD4+ and CD8+ cells continues to occur although at a lower rate [22]. Douek *et al.* in 2000 observed episomal DNA structures, markers of recent T-cell receptor rearrangement in thymic tissue, in T cells from aged persons [22], even if recent thymic emigrants were 10-100 fold reduced in the elderly as compared to infants [22]. Therefore thymic involution results in a reduced production of naïve T-cells with the gradual loss of the T-cell repertoire available against neoantigens [22].

The loss of naïve T-cells is associated with an impressive expansion of CD45Ro+ and memory CD8+ cells [23]. Memory cells have important functional differences from naïve T-cells. They have limited proliferative capacity, they express fewer costimulatory molecules like CD40 ligand and CD28 [23]. Moreover T-cells from elderly persons have a depressed synthesis of IL-2 limiting T-cell proliferation after stimulus by antigens [23]. Also the intracellular signalling pathway of T-cells is impaired in the elderly. Mitogen-activated protein kinase activation following T-cell interaction with antigen presenting cells is reduced [23].

Several studies report a shift from type 1 cytokine response (IL-2, IFN- γ , TNF) to a type 2 cytokine response (IL-4, IL-10) in elderly persons. Plackett *et al.* proposed that the altered lymphocyte response occurring in healthy aged individuals is a contributing factor to the increased incidence of mortality and sepsis after a traumatic injury in the elderly [24]. They showed an increase with age in the production of TH2 cytokines including IL-4 and IL-10 by splenocytes [24]. Similar results were obtained by Mascarucci *et al.* [25] and Sandmand *et al.* [23]. Sandmand *et al.* found a correlation between the percentage of T cells with TH2 cytokine expression and the *in vivo* expression of CD95 and CD45RO. Such age-related alterations in cytokine production may play a role in the reduced immune responses observed in elderly human populations [25].

Adaptive B-Cell Immunity

The age related impairments in adaptive T-cell immunity are associated with significant dysfunctions of the humoral immune response to neoantigens. B-cells and plasma cells gradually decrease with aging, at the same time immunoglobulin levels increase [2,26]. This increase regards especially immunoglobulin derived from B1 cells, while those derived from B2 cells are significantly decreased [27]. B1 cells produce polyspecific antibodies with low affinity for antigens and even autoantibodies including rheumatoid factor independently from T cells [27]. On the contrary, B2 cells, interacting with T cells, produce antibodies with high specificity for antigens [27]. The expansion of B1 cells with age is partially related to the higher IL-6 levels characteristic of the elderly, while the decrease in B2 cells is associated to impairments of the T-helper cells. In particular the reduced expression of costimulatory molecules on T-helper cells has been considered responsible for the depressed function of B2 cells [27]. Therefore elderly individuals have a decreased ability to produce specific opsonophagocytic antibodies against neoantigens. The production of antibodies against antigens previously presented to B cells is retained [2].

EFFECTS OF AGING ON SEPSIS INDUCED APOPTOSIS

Apoptosis is an active process leading to cell death mediated by programmed signaling pathways triggered by extracellular or intracellular stimuli [28]. Apoptotic cells have characteristic morphological changes including a shrinkage of the cytoplasm, membrane blebbing, compaction of the nuclear chromatin, chromosomal DNA fragmentation, and the formation of small vesicles, which are phagocytosed by macrophages and other neighboring epithelial cells [29]. The

cellular pathways leading to apoptosis include the caspase cascade and the stress-activated protein kinase pathways (Fig. 2) [28]. Caspases are specific proteases whose activation determines apoptotic cell death. Their activation may occur in two main ways: from the cell surface or from mitochondria [28]. TNF may activate the cell surface route of caspase activation [30]. In particular TNF-receptor 1 may link the TNF-receptor-associated death domain protein; this complex interacts with the Fas-associated death domain protein that activates caspase 8 and subsequently other caspases including caspase 3 [30]. Mitochondrial damage activates the mitochondrial route of caspase activation, in fact, when some mitochondrial proteins, including cytochrome c and other peptides enter the cellular cytoplasm, they can activate caspase 9 and 3, resulting in cellular apoptosis [31]. The stress-activated protein kinase pathway of apoptosis starts with the prolonged activation of mitogen-activated protein kinases involved in the intracellular transduction of many proinflammatory cytokines including IL-1 and TNF [32]. It is clear that sepsis may stimulate apoptosis both through the caspase pathway and the stress-activated protein kinase pathway.

There is evidence of a synergism between aging and sepsis in promoting apoptosis [33,34]. In 2004 Turnbull *et al.* studied the effects of age on sepsis-induced splenic and gut epithelial apoptosis in mice [33]. They concluded that the combination of infection and aging leads to a disproportionate increase in the apoptosis of rapidly dividing cells [33]. Mitochondrial dysfunction that may result in apoptosis is a hallmark of both aging and sepsis. It is well known that nitric oxide and other free radicals inhibit the mitochondrial electron transport chain, resulting in energy failure of the cell and mitochondrial disruption. In 2003 Escames *et al.* found that both aging and sepsis increase the mitochondrial production of nitric oxide and free radicals, stimulating mitochondrial nitric oxide synthase [34]. When lipopolysaccharide acts on aged mitochondria the production of nitric oxide is significantly higher than when it acts on young mitochondria. Therefore it seems that sepsis produces more pronounced inhibition of the mitochondrial respiratory chain and more severe mitochondrial damage causing cellular apoptosis in the elderly than in the young. The effects of aging on sepsis-related apoptosis help explain the increased incidence of

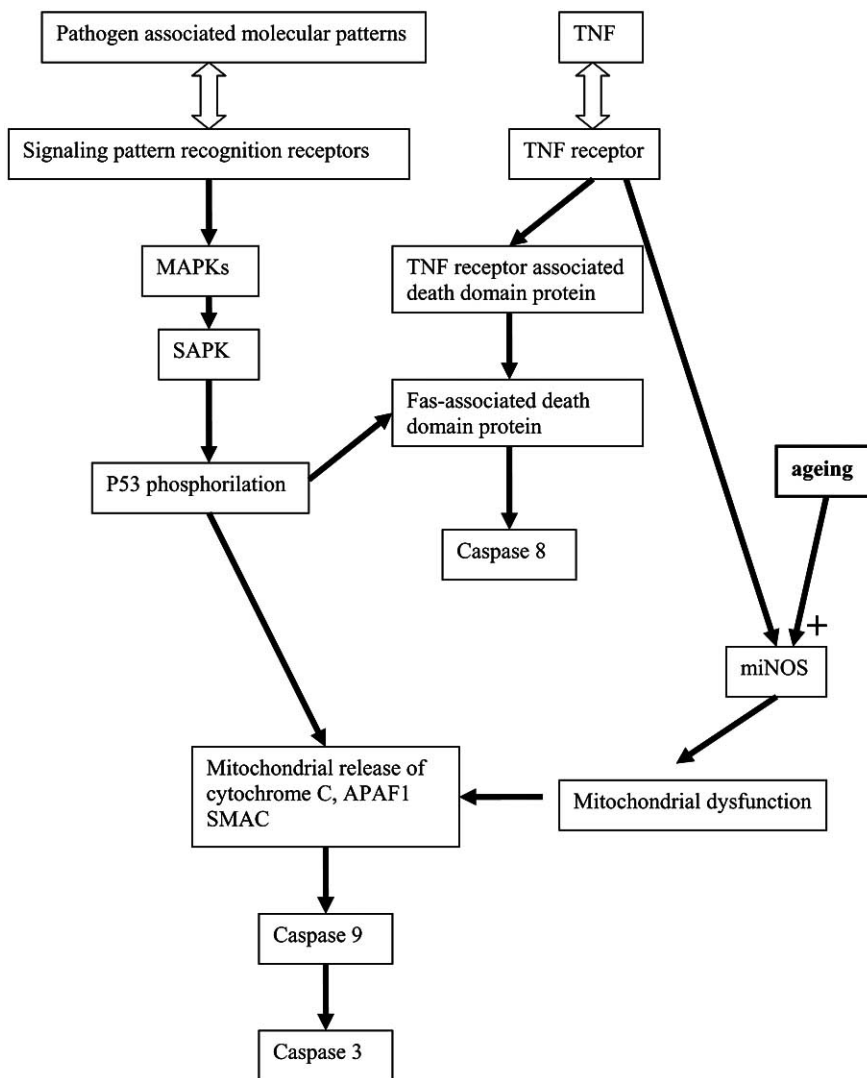


Fig. (2). Apoptotic pathways during sepsis.

multiorgan failure and mortality from sepsis in the elderly [34].

SEPSIS-RELATED COAGULATION ABNORMALITIES

As previously stated, severe sepsis is associated with a diffuse activation of the coagulation system throughout the microcirculation (Fig. 3) [2]. The coagulation and inflammation systems are interacting networks [2]. Proinflammatory cytokines, PAF and adherence molecules increase tissue factor expression, triggering the tissue factor pathway of the coagulation cascade and the production of thrombin and fibrin [35,36]. Proinflammatory cytokines increase the production of plasminogen activator inhibitor type 1, resulting in impaired fibrin degradation [37]. The activation of the clotting cascade and inhibition of the fibrinolytic pathway determine the spreading of clots in the microcirculation, resulting in tissue hypoperfusion during severe sepsis. On the other hand, the production of thrombin, factor Xa, and tissue factor-factor VII complexes promotes the inflammatory response because all these coagulation factors interact with specific protease-activated receptors on white cells, platelets and endothelial cells, inducing the production of IL-6 and IL-8 [38,39]. Moreover, fibrinogen may directly activate TLR-4 [40].

Aging by itself is associated with a procoagulant state [41]. With advancing age, an increasing number of healthy individuals have laboratory signs of heightened coagulation factor activity [42]. Mari *et al.* evaluated the activity of several coagulation factors in healthy centenarians and in adults [42]. Centenarians had higher values of several coagulation and fibrinolysis measurements than younger controls. Activated factor VII was increased in the plasma of centenarians as well as prothrombin, factor IX, factor X, and thrombin-antithrombin complexes. Increases in plasminogen activator inhibitor type 1 has also been found increased in the elderly [42]. Yamamoto *et al.* showed that endotoxin induces more plasminogen activator inhibitor type 1 in aged than in young mice. In these experiments the increased production of PAI-1 was correlated with larger stimulation of TLR-4 in older mice [37]. These observations may explain the increased risk of thrombosis associated with aging [37]. The combined impact of aging and sepsis on the coagulation cascade may

explain the greater efficacy of treatment with activated protein C in elderly patients than in younger ones [43]. Ely *et al.* evaluated both short- and long-term survival outcomes among 386 patients ≥75 years who were enrolled in the Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial [43]. They found that older patients with severe sepsis have higher short- and long-term survival rates when treated with activated protein C than when treated with placebo [43].

CARDIOVASCULAR INVOLVEMENT

Cardiovascular involvement associated with sepsis includes myocardial dysfunction and hypotension resulting mainly from failure of the vascular smooth muscle to constrict. Such vasodilatory shock is characterized by a poor response to vasopressor drugs and by high plasma catecholamine concentrations and activation of the renin-angiotensin system [44]. In this condition vasodilatation and hypotension are due to failure of the vascular smooth muscle to constrict. Several mechanisms have been proposed to account for this failure, including the death of vascular cells due to prolonged hypotension, inadequate oxygen extraction by the tissues, and increased activity of prostaglandins with vasodilator activity [44]. From a molecular perspective three mechanisms have thus far been implicated in this vasodilatory shock associated with sepsis: activation of ATP-sensitive potassium channels in vascular smooth muscle, activation of the inducible form of nitric oxide synthase, and deficiency of the hormone vasopressin probably caused by the depletion of its neurohypophysis stores after prolonged hypotension (Fig. 4) [44]. Vasopressors like angiotensin II and norepinephrine act by increasing the concentration of calcium in the cytosol. Calcium is released from intracellular stores and enters the cell from the extracellular space through voltage-gated calcium channels. Calcium activates the light chain of myosin kinase, producing vasoconstriction. Vasodilators such as atrial natriuretic peptide and nitric oxide activate the myosin phosphatase, and thus prevent vasoconstriction [45]. Membrane potential of vascular smooth-muscle cells may play a critical role in this process. Depolarization of the smooth muscle opens the voltage-gated calcium channels, increasing the cytosolic calcium concentration, whereas hyperpolarization closes these channels. Because sustained vasoconstriction requires extracellular calcium, membrane

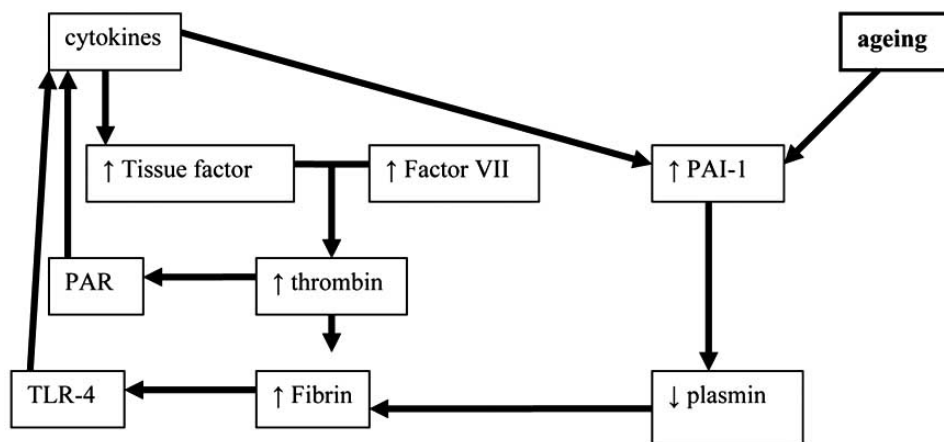


Fig. (3). Ageing and inflammation-coagulation network during sepsis.

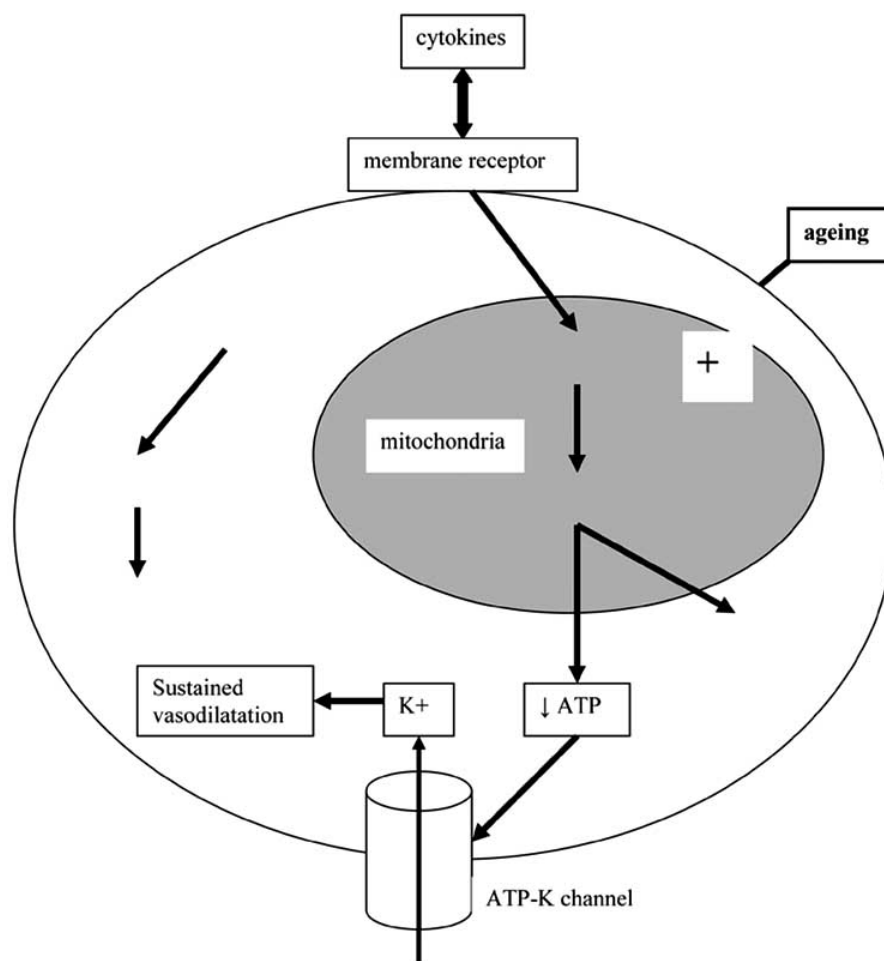


Fig. (4). Effects of aging on vasodilatation pathophysiology during sepsis.

hyperpolarization prevents vasoconstriction even in the presence of vasoconstrictor ligands. Potassium channels contribute to the membrane potential of vascular smooth-muscle cells [46,47]. ATP sensitive potassium channels open if the cellular concentration of ATP decreases, causing hyperpolarization and preventing vasoconstriction [47]. Such channels are activated during sepsis because of tissue hypoxia, cellular acidosis and mitochondrial dysfunction, and also through neurohormonal activators like atrial natriuretic peptide, calcitonin gene-related peptide, and adenosine [47]. Nitric oxide induced during sepsis can also activate these channels through a cyclic guanosine monophosphate dependent mechanism, and it can activate other potassium channels [48]. Aging is associated with a more severe vasodilatory shock during sepsis, probably because of increased mitochondrial dysfunction and nitric oxide production [34].

Sepsis-associated myocardial depression is due to several factors including TNF, nitric oxide and probably other inflammatory cytokines like IL-1 and IL-6 which have a negative inotropic effect [49,50,51]. Microcirculatory inflammation of the myocardium produces a local activation of neutrophils that result in cardiovascular tissue injury through a cytotoxic mechanism [52,53]. Saito *et al.* found an increased endotoxin induction of IL-1 and IL-6 in the cardiac endothe-

lium of aged mice [54]. Recently Rozenberg *et al.* [55] found that a low dose of endotoxin induces severe myocardial dysfunction in senescent rats. Rosas *et al.* demonstrated that advanced age is associated with augmented cardiac beta-adrenergic depression [56]. All these studies confirmed a significant increase in septic shock-related mortality during aging. This is the result of increased sepsis-related cardiovascular stress on pulmonary and cardiovascular systems with reduced physiological reserve and stress tolerance [56].

CLINICAL IMPACTS

The pathophysiological considerations discussed previously may explain why several clinical studies have shown that the epidemiology, clinical presentation and outcome of severe sepsis in the elderly is particular [57].

Girard *et al.* recently reviewed the epidemiology of sepsis in the elderly [57], founding an increase in the incidence of sepsis with increasing age. Angus *et al.* evaluated the epidemiology of sepsis in 192,980 patients, finding an incidence of 3 cases/1000 population [58]. When considering patients over 85, the incidence increased to 26 cases/1000 population, more than 100 times higher than that found among patients aging from 5 to 14 years old [58].

In regard to the microbiological pattern of sepsis in the elderly, Martin *et al.* found an increased risk of infections due to Gram-negative organisms in elderly patients, and an increased incidence of pulmonary and genito-urinary infections [59].

The clinical presentation of sepsis in the elderly is challenging to diagnose even when the signs of systemic inflammatory response are evaluated carefully [57]. Elderly patients often show an initial blunted inflammatory response that later becomes suddenly very severe with progression to septic shock [2,57,60]. Initial signs of systemic inflammatory response, like fever, may be blunted or absent in the elderly. Gleckman *et al.*, studying 192 patients aging more than 65 years old with bacteremia and 128 bacteremic patients below 65 years of age, found that fever was absent in 13% of elderly patients and in 4% of young and adult patient [61]. Castle *et al.* evaluated the trend of body temperature during 69 infective episodes in 26 elderly patients [62]. In 47% of the infective episodes the fever response was blunted with a peak body temperature below 101°F (38.3°C) [62], even if 89% of the infective episodes had a peak body temperature greater than 37.2°C. The authors suggested that a lower fever threshold be considered in nursing home residents [62]. Miller *et al.* investigated the possible pathogenesis of this blunted fever response founding a blunted hypothalamic response to TNF-alpha in the aged mice [63]. Other signs of systemic inflammatory response may be blunted as well [63]. In 1996 Chassagne *et al.* found statistically fewer symptoms in elderly infected patients than in young ones; a logistic regression analysis considering 16 common clinical or biological signs, showed four variables as significantly and independently associated with bacteraemia in the elderly: rapid onset of infection, fever, altered general state and clinical indication of the source of infection [60]. Other authors pointed out that non-specific clinical expressions of infection including delirium, weakness, anorexia, malaise, falls, urinary incontinence are common in elderly patients [57,64].

The switch to severe sepsis is usually associated with a more profound vasodilatory hypotension in elderly patients, probably because of a different response to pathogen-associated molecular patterns [2]. Krabbe *et al.* compared the response to endotoxin in aged and adult volunteers [65]. Aged volunteers had more severe and prolonged hypotension associated with a higher production of reactive C protein and TNF alpha [65]. Many factors could explain the severe cardiovascular involvement observed in elderly severely septic patients. Several studies documented an increased production of IL-6, IL-1 and nitric oxide during severe sepsis in elderly patients [66,68]. The increased total production of such cytokines challenges the observation that a single leukocyte of the elderly produces fewer cytokines [14,15,68]. A more diffuse involvement of leukocytes and of other cells able to produce such cytokines (like endothelial cells) in the elderly could explain this contradiction. IL-6 and IL-1 are well known factors reducing myocardial contractility, while nitric oxide is a powerful vasodilation mediator [49,51]. The increased amount of these mediators in the elderly acts on a cardiovascular system submitted to the pathophysiologic changes of aging and therefore with a reduced stress tolerance. The result is that the heart of an aged septic patient

may not be able to provide the increase in cardiac output required by the septic syndrome because of impending ischemic wall dysfunction, heart failure or aging associated diastolic failure.

A large number of prospective and retrospective studies have shown increased sepsis-associated mortality in elderly patients with values ranging from 20% to 40% [57,69]. The fact that age is an important factor in sepsis outcome is further confirmed by all the internationally validated severity scores which include age among the sepsis severity and mortality influencing variables. It is well known that the elderly have less tolerance to endotoxemia. Opal *et al.* measured plasma concentrations of endotoxin before starting therapy with an IL-1 antagonist [70]. Endotoxemia did not affect outcome in patients under 65 years of age, but significantly increased mortality in ones over 65. Tateda *et al.* confirmed this observation in an experimental study evaluating the response to endotoxin of aged and young mice [71]. They found greater endotoxin lethality among old mice that also had higher concentrations of TNF-alpha, IL-6 and IL-1 [71]. This different response to endotoxin in the elderly may derive from a different inflammatory response due to immunosenescence, more severe hemodynamic and respiratory impairment, reduced functional supply of many tissues and greater mitochondrial dysfunction resulting in enhanced apoptosis.

The outcome of patients surviving sepsis seems also more severe if they are elderly. In a recent trial Ely *et al.* found that 45% of patients >75 years who survived sepsis were transferred to a nursing home and 11% to another hospital [43].

THERAPEUTIC CONSIDERATIONS

Physicians should treat elderly patients with severe sepsis and septic shock according to the internationally recommended guidelines [72] while keeping in mind their peculiar pathophysiology. Treatment of sepsis includes not only pharmacologic therapy, but also other strategies such as source control and supportive therapies like fluid therapy, mechanical ventilation and artificial nutrition. Appropriate source control of infection is fundamental if a focus of infection amenable to surgical or interventional treatment is identified. Source control measures include removal of infected foreign bodies (intravascular catheters), drainage of abscesses or fluid collections and definitive management of anatomical derangements sustaining microbial contamination. Mechanical ventilation is indicated in case of severe respiratory failure. Protocols based on low tidal volumes have resulted in decreased mortality, duration of mechanical ventilation and IL-6 in patients with ARDS. Such protocols have been advocated for prevention of ALI and ARDS in septic patients.

Specific considerations are necessary regarding treatment of severe sepsis and septic shock in elderly patients:

Goal Directed Therapy

A recent randomized study demonstrated a significant reduction in mortality if early resuscitation is started as soon as severe sepsis is diagnosed aiming at central venous pres-

sure of 8-12 mmHg, mean arterial pressure >65mmHg, urine output >0.5mL/kg/h and central venous oxygen saturation >70% [73]. These targets were achieved with aggressive fluid therapy, dobutamine and hemotransfusions. These targets should probably remain the same in elderly patients, and there are several considerations about the means to achieve these targets. The increased cardiac output necessary during sepsis can be obtained in elderly patients mainly by increasing systolic output, because the heart rate increases less than in the young; tachycardia may not produce significant increases in cardiac output because of the diastolic dysfunction associated with aging [74]. The main mechanism available to the elderly patient to increase systolic output is the Starling effect produced by the increase in left ventricular preload [74]. Therefore it is crucial to maintain adequate cardiac filling when the aged patient needs to increase his cardiac output, like during sepsis. Although excess fluid administration should be avoided, under-resuscitation should also be avoided, therefore liberal amounts of intravenous fluids should be administered under central venous pressure monitoring during initial resuscitation to sustain organ perfusion, keeping in mind that older patients are often dehydrated. On the other hand, amines like dobutamine should be used with caution in elderly patients because of the risk of silent coronary artery disease and because the effective benefits of such amines is less pronounced in the elderly than in the young given the relative resistance to beta stimulation characteristic of the aged heart [56]. The role of hemotransfusion is a question of debate [73,75,76]. The target hemoglobin level in the absence of tissue hypoperfusion, active bleeding and coronary artery disease should be 7-9 g/dL according to a large trial published in 1999 [75]. In case of myocardial infarction hemoglobin levels of 10-11g/dL were associated with higher survival rates [76]. If hypoperfusion is underway the hemoglobin target should be around 10 g/dL [73]. Elderly people have a high prevalence of coronary artery disease that is often silent, this consideration should aim at a proper hemoglobin target.

Antibiotic Therapy

The general clinical picture of the elderly decreases the chances of an early diagnosis of sepsis. As soon as the diagnosis occurs, appropriate cultures should be obtained before antimicrobial therapy is initiated. In older patients it is often difficult to identify the source of infection due to the paucity of symptoms related to some kind of infection like those involving the urinary tract. Empirical antibiotic therapy should be started within one hour of the diagnosis of sepsis after culture sampling. Because inadequate initial antibiotic therapy is associated with poor outcome at all ages, the initial antibiotic therapy should have a broad spectrum against all probable pathogens [77].

Often sepsis is caused by multiresistant microorganisms in elderly patients [57]. They enter the microbial flora of older patients after repeated antibiotic exposure due to comorbid conditions, immunocompromised states, residence in nursing homes, repeated hospitalizations and use of invasive devices. The high incidence of sepsis due to multiresistant microorganisms in aged patients should guide the choice of initial empirical therapy toward combination therapy using antibiotics active against such microorganisms. Aging is

usually associated with a prevalence of Gram-negative infections, even if a high incidence of multiresistant Gram-positive strains has been observed in older patients. Therefore appropriate initial empirical therapy should address both Gram-negative and Gram-positive bacteria, including drug-resistant strains [57]. De-escalation to monotherapy can be considered once the causative organism has been identified.

In older septic patients pharmacokinetics and pharmacodynamics of antibiotics can be modified by age-related renal alterations, reduction in lean body mass and hepatic renal flow [78]. These abnormalities increase the risk of antibiotic-related adverse effects. Physicians should monitor antibiotic blood concentrations when possible to titrate the appropriate dose according to metabolic changes [78]. The concentration of time-dependent antibiotics (beta-lactams, glycopeptides, linezolid) should be maintained 2-5 times above the minimal inhibitory concentration (MIC) for the specific pathogen during 40-100% of the time between two consecutive boluses. This target could be achieved using a continuous intravenous infusion. Whereas concentration dependent antibiotics (metronidazole, quinolones, aminoglycosides) should have a maximum plasmatic concentration (C_{max}) at least 10 times the MIC for the specific pathogen. This can be obtained using high bolus dose. In particular, aminoglycosides, which are also concentration-dependent, are better administered once daily to reduce the risk of renal failure and cholear impairment.

Activated Protein C

A randomized trial published in 2001 demonstrated a significant reduction in mortality when activated protein C was used in the treatment of severe sepsis and septic shock⁴³. Such benefit involved aged patients as a consequence of their severe sepsis-related coagulation abnormalities. International guidelines recommend treating septic patients at high risk for death (APACHE score >25), with septic shock, dysfunction of at least two organs and sepsis-induced ARDS with activated protein C [72]. The pharmacodynamics of activated protein C include anticoagulant, profibrinolytic, anti-inflammatory and anti-apoptotic effects. These mechanisms may be particularly beneficial considering the pathophysiology of sepsis in the elderly which is associated with pronounced alterations of the coagulant, fibrinolytic and apoptotic systems, as previously stated.

Steroids

Improved mortality rates have been reported in patients with relative adrenal insufficiency treated with low-dose hydrocortisone [79]. Caution and appropriate dosing of glucocorticoid are suggested when considering aging-associated immunologic changes [57]. The use of high dose glucocorticoid results in immunodepression, poor glucose control and myoneuropathy, therefore this regimen is particularly contraindicated in elderly septic patients.

Glucose Control

International guidelines recommend the maintenance of blood glucose level <150 mg/dL with continuous intravenous infusion of insulin and glucose [72]. A previous trial demonstrated a significant reduction in mortality when the

blood glucose level was kept between 80 and 110 mg/dL in the postoperative period [80]. High glucose levels could impair immunologic response and enhance sepsis-related coagulopathy. The surviving sepsis campaign suggested a higher target of blood glucose level to avoid the risk of hypoglycaemia [72]. Such a risk is particularly common in elderly septic patients submitted to insulin infusion, therefore the target of 150 mg/dL seems to be safer in such patients.

Sedatives and Analgesics

Older patients usually experience anxiety, pain and delirium during sepsis, requiring sedatives and analgesic drugs. However, inappropriate use of these drugs can delay the weaning from mechanical ventilation [81, 82]. Sedatives and analgesics should be administered under a sedation scale monitoring, using intermittent bolus regimens or daily interruptions of continuous infusion sedation [72]. Benzodiazepines may produce paradoxical reactions in older patients with anxiety and psychomotor agitation. Neuroleptic drugs are indicated in case of delirium in aged septic patients.

CONCLUSIONS

Aging is associated with a peculiar pathophysiology of sepsis involving immunosenescence with cardiovascular, metabolic, apoptotic, clinical and therapeutic implications [2,57]. Physicians should remember that they are not confronting sepsis, but always septic patients. Sepsis is a syndrome with important pathophysiological and clinical differences, depending on the specific characteristics of affected patients. Aging is probably one of the most important of these characteristics including also genetic polymorphisms. The PIRO approach to sepsis has recently included such considerations, even if a more diffuse awareness should be achieved in clinical practice [83,86]. The demographic changes going on today will probably increase the incidence and mortality of sepsis since it will affect older patients. Therefore, research on therapeutic strategies with particular benefits to this group of patients should be encouraged in the near future.

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