Role of Immunosenescence in Infections and Sepsis in the Elderly

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Abstract

It is well known that infections and sepsis are increased in elderly subjects, and that the immune system changes with age. The question arises whether dysfunctionality of the immune system, which is most of the time is also called immunosenescence, contributes to this increased incidence of infections in elderly and if so, how. As the immune system evolved to protect against infection, the role of aging is likely to be important for the increased occurrence, progression, and outcome of infections and sepsis in the elderly. However, the intricate multiple mechanisms that contribute to this increase are difficult to dissect with certitude and remain controversial. Immune alterations most likely to contribute to this overwhelming clinical burden of infections and sepsis will be reviewed in this chapter.

Keywords

Infections · Sepsis · Elderly · Immunosenescence · Inflamm-aging · Vaccination

Introduction

It is well known that infections and sepsis are increased in elderly subjects and that the immune system becomes in many ways dysfunctional with aging. The question arises whether this dysfunction, described as immunosenescence, contributes to this increased incidence of infections and if so, how. The answer would seem to be a priori in the affirmative, but it is very difficult to ascertain a direct relation between these two phenomena. Immunosenescence differentially affects the various components of the immune system; moreover, many extrinsic factors such as nutrition, chronic diseases, chronic antigenic stress, or hormonal changes also contribute to immunosenescence. Furthermore, aging is associated with a low-grade inflammatory state, often designated as Inflamm-aging that might be

causally involved in inappropriate responses to infection. It is still a debate what is the exact relationship of the immunosenescence with the Inflamm-aging that they are the two sides of the same process or one is the determining cause of the other creating a vicious cycle.

Infections in the Elderly

Typical bacterial infections including respiratory tract, urinary tract, skin, and gastrointestinal infections are a common problem in older adults (Castle et al. 2007). Not only bacterial, but viral infections such as lung infections due to influenza A or respiratory syncytial virus, or reactivation of herpes zoster are also very common in elderly. Moreover, pseudomembraneous colitis related to microbial colonization by Clostridium difficile or methicillin-resistant Staphylococcus aureus (MRSA) in severely ill patients treated with antibiotics is becoming an important health issue in elderly people (Castle et al. 2007). One of the most significant public health problems is influenza virus infection, which causes 10,000–40,000 excess deaths in the USA, of which 90% are in persons over 65 years (Castle 2000). Influenza is the fifth leading cause of death among people aged 50 and older, and this is a major target of vaccination campaigns (Kovaiou et al. 2007; Nichol et al. 2007). The incidence of pneumococcal infections increases dramatically in people over 75 years of age (Vila Corcoles 2007; Askim et al. 2016). Mortality is higher in the elderly and rises with increasing age, approaching almost 80% in those over 85 years of age. Rates of bacteremia and meningitis from pneumococcal infections are also higher in the elderly (Pawelec 2006). The incidence of herpes zoster is also greater in people over 75 years of age (Oxman and Levin 2008). Not only the incidence and prevalence of infections are increased in the elderly but also the consequences and the burden in terms of morbidity and mortality. The problem of infection is even greater in elderly nursing home residents, who are particularly vulnerable to infections. In addition to decreased immune responsiveness, malnutrition, and chronic diseases, long-term care facilities themselves provide environments that promote infectious outbreaks (Girard and Ely 2007). Elderly people in nursing homes suffer infections due to urinary catheters more often and have more frequent oropharyngeal colonization with Gram-negative bacilli (Tana and Hanada 2010). Nearly one-third of persons 80 years of age and older live in nursing homes where antibiotic resistance is a growing problem (Girard and Ely 2007) and residents who are infected are at a higher risk of mortality.

Sepsis in the Elderly

Sepsis is defined as the generalized, inflammatory host response to infection. Most of the time, it appears as a life-threatening clinical situation. It is not a single disease but is an intricate and heterogeneous process expressed through the interaction of a complex network of biochemical and cellular mediators and amplification cascades.

Its severity is mainly determined by the causative agent, the patient's genetic background, and the rapidity of medical intervention (Marshall et al. 2003). This inherently complex process, reflecting the dynamic interaction of an acute, life-threatening infection with the adaptive protective mechanisms of the host and its environment, is frequently modified often in an unpredictable manner by the effects of advancing age, sex, and/or acute and chronic underlying disorders (Dhainaut et al. 2005).

Each year in the USA, nearly 2500 cases of sepsis occur per 100,000 persons aged 85 years, with elderly persons being much more likely to suffer sepsis and bacteremia than younger subjects (Girard and Ely 2007; Martin et al. 2006). Incidence rates of sepsis increased 20.4% faster among elderly persons than among younger persons from 1979 to 2002 (mean increase per year, 11.5% vs. 9.5% $p < 0.001$). Other large studies have reported that the incidence of sepsis and bacteremia increase with older age (Baine et al. 2001; Askim et al. 2016). Furthermore, the microbiology of these infectious diseases is also different in the young and old patients (Girard and Ely 2007). Thus, in contrast to young sepsis patients, most of these disorders in the elderly are due to Gram-negative organisms. Escherichia coli was found to be the responsible agent in most cases in the elderly, while in young subjects, Staphylococcus aureus was the main pathogen in community-acquired bacteremia (Diekema et al. 2002). The causative agent tends to be different in nosocomial bacteremia, in that in the elderly, the most frequent pathogens is MRSA, while in young patients, this is again S. aureus without drug resistance. These differences in the microbiology of sepsis with age are partly explained by the source of infection leading to sepsis among the elderly. Urinary tract infections due to Gram-negative bacteria are more frequently the source of bacteremia or sepsis in elderly than in young patients. In a study of community-acquired bacteremia, it was found that patients 65 years of age were more likely than younger patients to have the urinary tract as the source of infection (Lark et al. 2001). These data suggest that the elderly could be more susceptible to Gram-negative bacterial infections than young subjects due at least partly to changes in immune functions with aging (Martin et al. 2017). Recent findings support this line of thinking. Indeed, it was reported that the numbers of CD4/8 + CD28+ T cells were strongly decreased in elderly septic patients; conversely, the numbers of CD4 + CD25 + Foxp3 + T cells were increased, especially in nonsurviving elderly septic patients (Inoue et al. 2013). Also, the expression of PD-1, an inhibitory receptor, was increased on lymphocytes of elderly septic patients compared to healthy elderly patients (Inoue et al. 2013), suggesting that the negative regulation of T cell activation is dysregulated in elderly septic patients. Functionally, CD4+ T cells isolated from elderly septic patients and activated ex vivo produced less IL-2 and proliferated less than equivalent T cells isolated from healthy control patients and adult septic patients (Inoue et al. 2014). As for B cells, the only study made with elderly septic patients reports that serum IgM levels are lower in septic and elderly healthy patients than in adult healthy patients; interestingly, IgG levels are not influenced by sepsis in elderly patients, as opposed to adult patients (Suzuki et al. 2016). Finally, platelet–monocyte aggregation, a marker of in vivo platelet activation, was shown to contribute to the pathophysiology of septic syndromes. In elderly septic patients, increased levels of platelet–monocyte

aggregation correlated with an increased risk of mortality (Rondina et al. 2015). Interestingly, platelet–monocyte aggregation levels were actually lower in elderly patients compared to adult patients (Rondina et al. 2015). In addition, elderly septic patients were more susceptible of secondary infection to Gram-negative bacteria and fungi after sepsis (Inoue et al. 2014; Suzuki et al. 2016). The authors conclude that prolonged elevation of serum IL-6 in elderly septic patients (Inoue et al. 2014), which suggests continued inflammation in these patients relative to adult septic patients, explains, in part, their findings. Another group, whose findings showed that plasma IL-6 is significantly increased in nonsurviving elderly septic patients compared to surviving elderly septic patients (Rondina et al. 2015), substantiates this. Together, these data show that older age is independently associated with an increased likelihood of severe sepsis and mortality.

Alterations in the Immune System in Aging that Could Favor the Increase of Infections and Sepsis

Innate Immune System

The innate immune system includes neutrophils (PMN), macrophages, and NK cells. These cells are the first to encounter any type of infection, whether bacteria or viruses. They recognize pathogens by means of their nonpolymorphic conserved pattern recognition receptors (PRRs) and discriminate between invaders representing a danger for the organism and those not pathogenic. One of the most studied groups of PRRs belongs to the Toll-like receptor family (TLRs). There are more than 11 members of this family, including TLR4 reacting to Gram-negative bacteria, TLR2 reacting to Gram-positive bacteria, and TLR3 and TLR9 reacting to viruses. Stimulation of innate immune system cells via TLRs initiates a complex signal transduction cascade, which can result in proinflammatory activation through translocation of NF-κB to the nucleus (Krishnan et al. 2007). This renders the cells of the innate immune system more potent in their effector functions, such as phagocytosis, free radical production, and intracellular killing, which result in the destruction of the invader. Such activation may also initiate and modulate adaptive immune responses either by antigen presentation or secretion of different cytokines and chemokines, perhaps as a mechanism required if the innate immune response fails to clear the pathogen.

Aging affects components of the innate immune system differently. Some functions are well preserved, such as phagocytosis, while others are decreased, such as chemotaxis, intracellular killing, and free radical production (Montgomery and Shaw 2015). Furthermore, even if the number of TLRs expressed on the cell surface appears unchanged, their signalling is altered, leading to dysregulated intracellular activation of proinflammatory cytokines (Fulop et al. 2004; Hazeldine et al. 2014). Furthermore, the persistence of infections due to failure to clear the pathogen may result in persistent, chronic, activation. Keeping with this, PMN levels were significantly increased 7 days after diagnosis of sepsis in nonsurvivors compared to survivors in elderly patients (Inoue et al. 2013).

Adaptive Immune System

The adaptive immune system responds specifically to a unique antigen via antigenic presentation. The response is either humoral via B-lymphocyte antibody production or cellular via T cell activation. The T cell compartment is divided into helper (CD4+) and effector subsets (mainly CD8+). B and T cells also responding to antigens via specific cell surface receptors that initiate signalling cascades, leading to their activation. There could also be chronic antigenic activation in this compartment mainly by latent viruses such as CMV or herpes zoster (Vasto et al. 2007; Koch et al. 2007; Vescovini et al. 2007). Furthermore, a network of cytokines plays a major role in orchestrating a coordinated adaptive immune response via T and B cells. T cell functions are the most altered with age (Pawelec 2006; Castle et al. 2007). Following antigenic stimulation, the clonal expansion of T cells is decreased with age due to altered IL-2 production. There is also a shift from naïve T cells towards memory T cells (Effros 2004). This shift is partly explained by the involution of the thymus, leading to decreased output of naïve (virgin) T-lymphocytes. One other very important factor seems to be chronic CMV infection, as mentioned above. This leads to the oligoclonal expansion of CD8+ T cells in the elderly, the accumulation of which, in the form of apoptosis-resistant anergic effector CD8+ memory T cells, may have far-reaching consequences. These cells may fill the immune space and even suppress the function of the remaining naïve CD4+ T cells (Sansoni et al. 2008; Ely et al. 2007; Gruver et al. 2007). This leads to decreased recognition of novel antigens and in consequence a decreased ability to respond to not previously encountered pathogens. Another alteration, limiting the response of T cells to stimulation, is altered intracellular signalling following ligation of the TCR and CD28 coreceptor (Larbi et al. 2011; Fulop et al. 2014). All these alterations lead to a dysregulated adaptive immune response with aging. Evidence for the clinical importance of viral persistence along with other immune parameters has been provided from longitudinal studies of subjects above 85 years, where it was observed that the increased anti-CMV Ig levels correlated negatively with survival (Vasto et al. 2007; Koch et al. 2007; Vescovini et al. 2007). Moreover, these subjects had a lower response to vaccination.

Low-Grade Inflammation: Inflamm-Aging

An apparent disequilibrium between the relatively reactive innate immune response and the altered adaptive immune response with aging leads to the presence of a low-grade inflammatory status with aging (De Martinis et al. 2005). The cause of this low-grade inflammation is multifactorial. One of the most important is chronic antigenic stimulation. The antigen can be exogenous, such as bacteria or viruses, or endogenous like the various posttranslationally modified macromolecules such as DNA or proteins. They can be modified by oxidation, by acylation, or by glycosylation. Such altered molecules can stimulate the innate immune response, mainly macrophages via TLRs, thus contributing to sustaining a proinflammatory state (Guigoz et al. 2008). This is measurable in some circumstances as increased circulating levels of IL-6, IL-1β, or

TNFα. These modifications may also result in the stimulation of adaptive immune responses, recognized in an extreme form by an inverted CD4:CD8 ratio, caused by an overwhelming expansion of CD8+ cells (Wikby et al. 2008). All these changes contribute to a decreasingly effective immune environment that seems not to be able to respond appropriately to new infectious agents.

How Can Immunosenescence Contribute to Increased Infections and Sepsis in the Elderly?

Because underlying disorders are more frequent in the elderly, the role of age is crucial in delineating the true influence of underlying disorders on the host response and susceptibility to infections (Tables 1 and 2). Many large epidemiological studies

Table 1 The most significant functional alterations of the immune system with aging potentially implicated in the increased infections and sepsis

Innate immune response	Neutrophils and monocytes/macrophages
	↓ROS production
	↓Intracellular killing
	↓TLR signalling
	Dendritic cells
	↓Antigen presentation
	NK cells
	↓Decreased effector functions
Adaptive immune response	T cell antigenic response
	↓Proliferation
	↓Th I response: IL-2, IFNy
	↑Th2 response IL-4, IL-5, IL-10, IL-12
	↓Delayed type hypersensitivity
	↓T cells inducers of suppression
	↓T cell repertoire
	↓Signal transduction: early, intermediate, and late events
	T cell subpopulations
	↓Naive T cells
	↑Memory T cells
	T cell apoptosis
	↑CD4+ T cell apoptosis
	↓T cell repertoire CDS+ T cell apoptosis
	B cell antigenic response
	↓B cell repertoire
	↓Antibody quality?
Low-grade inflammation	Cytokines
	↑Proinflammatory cytokines: IL-6, TNF α
	↑Anti-inflmmatory cytokines: IL-10

Table 2 The most significant external factors with aging potentially implicated in the increased infections and sepsis

Malnutrition	Macronutrients
	↑Lipids
	↑Carbohydrates
	↓Proteins
	Micronutrients
	↓Zinc, Selenium
	↓Vitamins: vitamin E, vitamin C
	↓Antioxidants
Chronic diseases	Diabetes mellitus type 2
	Cardiovascular diseases: congestive heart failure
	Dementia
	Autoimmune diseases
	Pulmonary diseases: COPD
	Cerebrovascular diseases
	Cancers
Frailty	Low-grade inflammation
	↑Proinflammatory cytokines: IL-6, TNFa
Chronic antigenic stress	Chronic infections: CMV, EBV, herpes zoster
Neuroendocrine changes	↑Cortisol
	↓**DHEA**, growth hormone

now demonstrate that age is related to the occurrence (Angus et al. 2001; Martin et al. 2003) and prognosis of infection.

Contribution of the Intestinal Mucosal Defense

The barrier functions of the mucosal components including sIgA, mucins, defensins, gastric acid, and epithelial integrity may be seriously compromised with aging (Guigoz et al. 2008). The result of these alterations is that this first line of defense is no longer very efficient at excluding extracellular pathogens or sustaining protective commensals, which can even become pathological. However, there are still very few data regarding how mucosal immunity changes with age and influences the incidence of infections.

Contribution of the Innate Immune Response

Alterations in the innate immune response with aging as discussed earlier may greatly contribute to the increased incidence of infections and sepsis with aging. Decreased chemotaxis in response to chemokines results in poorer accumulation of the cells necessary for first line defence, including PMN (Fulop et al. 2004; Montgomery and Shaw 2015). Lower production of reactive oxygen species by

PMN and macrophages detracts from the clearance of pathogens. The presentation of antigens by dendritic cells seems to be fairly well maintained in healthy elderly, but there may be subtle differences, as well as the speed of processing being decreased (Castle et al. 2007; Castle 2000). However, elderly nursing home patients with significant chronic illness do have impaired functions of antigen-presenting cells (Castle 2000). The exact role of NK cells in the increased infections seen with aging is still controversial, as their exact functional changes with aging have not been determined exactly.

The decreased functions of PMN are particularly important in this setting. These cells are the first line of defense against infection. There is a complex process prior to PMN arrival at the site of invasion, including rolling, adherence, diapedesis, and chemotaxis. This process is relatively well conserved in aging, although chemotaxis may be compromised. Most importantly, the production of reactive oxygen species (ROS), playing a crucial role in intra and extracellular killing, is altered. It was shown that various Gram-positive bacteria ingested by PMN were not to be destroyed as efficiently as in young subjects (Fulop et al. 1985; Tortorella et al. 2007). Together, these data reinforce the notion of an important contribution of altered innate immune responses to the increased incidence of infections with aging.

As part of innate immunity, the proinflammatory response to infection is not diminished in the elderly, may contribute to the increased proinflammatory state commonly observed (Dhainaut et al. 2005). However, it should be mentioned that in SENIEUR elderly subjects, selected for exceptionally good health, this low-grade inflammation is practically nonexistent. This state of "Inflamm-aging" as it has been dubbed seems to manifest by an increase in the IL-6 level, which may be a reliable marker for functional disability and a predictor of disability and mortality in the elderly (Ferrucci et al. 1999; Maggio et al. 2006). Indeed, it was reported that activation of the coagulation (D-dimer) and the inflammatory (IL-6) pathway at baseline is associated with mortality and decline in function (Cohen et al. 2003). Aging is also associated with inadequate response to infections and sepsis-related stress. Monocytes from elderly patients undergoing surgery produced more TNFα than those from younger patients (Ono et al. 2000). After challenge with LPS in healthy young and elderly volunteers, the latter showed more prolonged fever response than in younger controls and levels of TNFα and soluble TNF receptor I levels were higher in the elderly (Krabbe et al. 2001). This study suggests that aging is associated with an altered host response with initial hyperactivity and a sustained secondary anti-inflammatory response. Elderly persons with pneumococcal infections also show prolonged and exaggerated cytokine responses, compared with those of younger persons (Bruunsgaard et al. 1999). Higher levels of proinflammatory cytokines, such as TNFα and IL-6, have been observed in elderly patients with sepsis when compared to young subjects (Marik and Zaloga 2001). In sepsis, these cytokines and others generated in response to toxic microbial stimuli activate leukocytes, promote leukocyte-endothelium adhesion, and induce endothelial damage. Indeed, sepsis can be conceptualized from the Inflamm-aging aspect as an extreme, uncontrolled, and somehow adaptive reaction of the aging dysregulated innate immune system.

Contribution of the Adaptive Immune Response

Aging is associated with dysfunction of T cell mediated adaptive immunity. Thymic involution together with chronic antigenic stimulation decreases the number and repertoire of naïve T cells, which leads to an inability to respond appropriately to a new antigen. This is correlated with an expansion of memory CD8+ T cells that fill the "immune space" due to their resistance to apoptosis. Moreover, they may suppress the retained CD4+ T cell response. It is also well recognized that the B cell-mediated humoral response is also decreased, contributing to the increase of infections by reduced specific antibody production, by reduced affinity and shrinkage of the B cell repertoire. As well as B cell intrinsic changes, decreased CD4+ T cell help contributes to these alterations. Furthermore, it was also recently shown that increasing age has a significant impact on the memory CD8+ T cell response to respiratory virus infections (Ely et al. 2007). There is a significant loss of effector memory cells from peripheral sites over time which may reduce the immediate response of memory T cells to secondary challenge. However, this is efficiently counteracted in part by the long-term maintenance of large numbers of memory CD8+ T cells in the secondary lymphoid organs and the progressively increasing capacity of these cells to generate proliferative recall responses (Woodland et al. 2001). Overall, it appears that T cell memory is not only maintained for long periods of time but may also be enhanced in the face of an age-related decline in the capacity of the immune system to respond to new pathogens.

Contribution of the Low-Grade Inflammation

The low-grade inflammation (Inflamm-aging) is considered a hallmark element of immunosenescence, leading to (most of) its clinical consequences. This state favors the development and progression of other age-associated chronic diseases, such as atherosclerosis, neurodegeneration (dementia), type 2 diabetes, metabolic syndrome, and congestive heart failure (De Martinis et al. 2005; Guigoz et al. 2008). It is well recognized that these diseases contribute to the further deterioration of defense mechanisms and thus patients suffering from chronic diseases are more susceptible to infections such as influenza or pneumonia. Hence, the severity of infectious diseases is greater in patients with chronic underlying disorders compared to healthy elderly subjects. The presence of one or two chronic illnesses such as emphysema, diabetes, cardiovascular diseases, chronic renal or hepatic failure is associated with a 40- to 150-fold increase in the basal incidence rate of influenza pneumonia. Hospital mortality is also related to severity of the underlying chronic diseases, including cardiovascular insufficiency, chronic obstructive pulmonary disease, and kidney failure. This is even more striking in nursing home settings.

Furthermore, low-grade inflammation plays a specific role in metabolic disorders of the elderly. The production of proinflammatory cytokines affects insulin resistance and muscle wasting (sarcopenia). This leads to a dramatic increase of diabetes in elderly subjects even if they are not obese. Moreover, this proinflammatory state contributes to the appearance of frailty as a clinically well-recognized physiological syndrome (Fried

et al. 2001). Most of the metabolic alterations related to low-grade inflammation can be also found in frailty. Thus, frailty seems to be in a continuum with aging before the development of specific diseases. It is also known that frail individuals are more prone to infections than those not suffering from this syndrome. The low-grade inflammation, metabolic alterations, malnutrition, chronic diseases, and sarcopenia are all concomitantly interacting to cause the increase of infections in the elderly.

The low-grade inflammatory status can even have a paradoxical effect in favoring the development of infections. "Overstimulation" might induce a compensatory anti-inflammatory overreaction (e.g., IL-10, IL-13), which could further impair immune responsiveness toward new antigens.

Response to Vaccination

To date, approximately 26 different infectious diseases can be prevented by vaccination, influenza being one of them (Herndler-Brandstetter et al. 2006). However, as a result of age-associated immune alterations, the elderly generally have a poorer response to vaccination than the young (Nichol et al. 2007; Lang and Aspinall 2014; Del Giudice et al. 2015). This correlates with decreased levels of protective antibodies following influenza vaccination (Pawelec 2006). Cell-mediated immunity represented by the CTL response, which may be even more important for protection than antibody, is decreased too (Van Damme et al. 2013). Not only is the vaccine response impaired in the elderly but even when it seems adequate, protection from infection is still less than in young subjects. This is probably related to the decreased ability of formed antibodies' to neutralize viruses. Nevertheless, despite this low efficacy of the immune response, it should be emphasized that vaccination in elderly subjects is efficacious in reducing adverse events. Moreover, recently it became evident that new vaccines applied with adjuvant to elderly such as the herpes zoster virus vaccine was as efficient even in elderly over 80 years of age as in young subjects (Lal et al. 2015). Once again, the question arises whether there exists a true "immunosenescence" or just the vaccines are not adequate/adapted to the elderly.

An underlying chronic illness or frailty dramatically increases the risk of influenza infection as well as impairing the response to vaccination. One study on vaccine responses in nursing home residents demonstrated that only 50% of vaccines generated an adequate response based on the definition of a fourfold increase in antibody titers (Sato et al. 2005). However, this population is one of the most targeted for vaccination, taking into account the clinical efficacy of vaccination in elderly subjects.

Conclusion

Immune dysfunction, mainly in the T cell compartment, is associated with age even in the healthiest elderly. The cause of this dysregulation is certainly multifactorial. The results of these alterations are obvious in certain clinical situations such as

infections. The role of aging is important for the increased occurrence, progression, and outcome of infections and sepsis in the elderly. However, the intricate multiple mechanisms that contribute to this increase are difficult to dissect with certitude and remain controversial. Nevertheless, the clinical burden most likely resulting from such immune dysregulation is overwhelming. Strategies should be developed in order to modulate the immune response in such a way that morbidity and mortality caused by infectious disease in the elderly is decreased. More effective vaccination strategies must be and currently are being developed. Other solutions should be also rapidly sought and implemented to improve the quality of life of the elderly in the rapidly increasing elderly populations of the developed countries.

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