



## Future challenges in analysis and treatment of human immune senescence

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Elsewhere in this issue authors describe the decline in immune function with age that might produce a mild to moderate immune deficiency; however, what is observed in geriatric medicine is an immune deficiency that is more striking than would be predicted by the modest changes that are caused by normal aging. The increase results from the contributions from comorbid illnesses, medications, or malnutrition. Therefore, a more severe immune deficiency and resultant health consequences are frequently observed.

Typically, these consequences are an increased susceptibility to certain infections, decreased capacity to respond to certain vaccines, increased paraproteinemia and other signs of dysregulated immunity, and possibly an increased incidence of certain types of malignancy. To reverse such untoward consequences concerted effort has been made over several decades to enhance immune function in older people. In the current article, the authors briefly examine the nonaging causes of immune deficiency in the elderly and outline previous and current efforts at immune reconstitution, including the health-promoting effects of exercise and optimal nutrition.

### **Secondary causes of acquired immunodeficiency in old age**

In contrast with the normative changes that may result in a mild, idiopathic acquired immunodeficiency with aging, a variety of secondary causes of acquired immunodeficiency occur in the elderly that may be severe, yet reversible (Box 1). Discriminating secondary causes of immunodeficiency from normal, age-related changes represents an important clinical distinction as many of these causes are reversible and the associated immune deficiency may be causally related to

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**Box 1. Causes of immune deficiency in the elderly**

Immunesenescence (aging)  
Comorbid illness  
Medications  
Depression  
Malnutrition  
Sedentary life style

susceptibility to infection, altered presentation of infection, or inadequate response to usual therapy.

The effects of malnutrition on the immune system may be profound, and clearly increase the risk of infection in the elderly [1]. Immune deficits in the undernourished, ambulatory elderly may be reversed by nutritional supplementation [2]. Malnutrition affects up to 50% of the hospitalized elderly and is associated with poor acute care outcomes, including death among the hospitalized elderly [3–6]. Severe protein, calorie, vitamin, and elemental deficiencies, such as zinc (a cofactor for the function of thymic hormone), may cause immunodeficiency and poor outcomes in response to infection [7]. An absolute lymphocyte count less than 1500 cells/mm<sup>3</sup> generally indicates some degree of malnutrition; a count less than 900 cells/mm<sup>3</sup> indicates severe malnutrition and immunodeficiency [8]. Chronic illnesses, such as cancer, congestive heart failure, and Alzheimer's disease, may be associated with progressive cachexia despite adequate food intake, and may be mediated by proinflammatory cytokines. Dysregulation of these factors may occur as a feature of normal aging [9] or in association with comorbidities. Under either circumstance, their increased presence is likely to contribute to the frail phenotype that is apparent in many of advanced age. Despite adequate nutritional intake, malnutrition affected 50% of patients with dementia and was associated with a fourfold increase in infections [10].

Because elderly people frequently use several medications, drug-induced acquired immune deficiency is probably far more common than is generally clinically recognized. Numerous commonly-used drugs cause neutropenia and lymphocytopenia [11,12]. Analgesics, nonsteroidal antiinflammatory agents, steroids, antithyroids, antibiotics, antipsychotics, antidepressants, hypnotics/sedatives, anticonvulsants, antihypertensives, diuretics, H<sub>2</sub> blockers, hypoglycemics, and other medications (such as allopurinol) commonly prescribed in old age may suppress the inflammatory immune responses. T lymphocytes have calcium channels, and cholinergic, histaminic, and adrenergic receptors, all of which may have effects on immune function [13]. Hypogammaglobulinemia also may be induced by medications [14]. Medications may also be associated with an impaired [15] or enhanced response to vaccination [16].

Psychosocial isolation, depression, and stress are probable causes of immune dysfunction in old age [17]. There is an increased incidence of cancer during periods of psychosocial stress and depression related to bereavement [18,19].

Furthermore, social isolation and marital discord may impair immune function has been documented [20,21]. Chronic stress in the form of caregiving for a demented spouse also reduces influenza vaccine response [22]. Interventions to enhance social contact improve immune function, as recorded by a variety of laboratory measures [23]. Immobility also may cause immune dysfunction, and exercise may maintain function in old age in animals and humans [24,25]. These aspects of psychoneuroimmunology obviously have particular relevance in the interdisciplinary practice of geriatric medicine in which psychosocial problems are common.

### **Immunesenescence and infections**

Probably the most profound effect of immunesenescence in old age is an increase in the morbidity and mortality from infections. Clearly, the rates of several infections and their morbidity and mortality increase with age [26], particularly influenza, pneumonia, urinary tract infections, skin infections, tetanus, and reactivation of latent infections (eg, herpes zoster, tuberculosis). An increase in hospital-acquired and nursing home infections in the elderly also is noted. In addition to immune impairments, a decline in primary host defenses also contribute to the increased rates of infection, such as a reduced cough reflex leading to aspiration pneumonia, urinary and fecal incontinence predisposing to urinary tract infections, and immobility predisposing to wound infections. Unusual organisms may also be the result of previous antibiotic treatment that causes the expression of resistant organisms. Infections may present atypically (eg, without fever or localizing symptoms) [27] and run a more prolonged course [28]. Elderly patients may not present with typical signs of infections, such as spiking fevers, leukocytosis, prominent inflammatory infiltrates on chest radiograph, or rebound tenderness in patients with an acute abdomen. Lower baseline temperatures may require the need for monitoring the change in temperature, rather than the absolute temperature, in old age [29] and changes in mental status may be the only indicator of local or systemic infection.

Older individuals, particularly the frail elderly, may fail to respond normally to therapy for infection, and may present with infections secondary to unusual organisms, recurrent infections with the same pathogen, or reactivation of quiescent diseases, such as those caused by tuberculosis and herpes zoster virus. The impaired immune and inflammatory response in old age changes the clinical expression of infections. Typical signs of infection are often absent, and a high index of suspicion is necessary for detecting infection in older individuals. Three specific viral infections are given special attention because of current research activity in the context of immune reconstitution.

#### *Influenza*

Most of the significant morbidity and excess mortality during influenza epidemics occurs in older adults [30]. Age alone is a significant risk factor for

severe complications of influenza [31]. It is widely believed that much of the increased susceptibility of elderly people to influenza and its complications is attributable to immunologic factors, including reduced antibody responsiveness and influenza-specific, cell-mediated immunity. The role of humoral immunity, especially in the form of neutralizing antibody, is perhaps most important for preventing and limiting the initial infection rather than promoting recovery [32]. T-cell-mediated responses seem to be more important and are primarily involved in postinfection viral clearance and recovery; influenza-specific cytotoxic T-lymphocyte (CTL) activity correlates with rapid clearance of virus in infected human volunteers, even in the absence of detectable serum antibody [33], and was experimentally confirmed in adoptive transfer of influenza-specific CTL experiments using the mouse model [34,35]. Influenza-specific antibody declines with age, whether due to natural infection or vaccination [36–38]; this presumably translates to an increased risk of influenza infection. Despite all of the changes that occur with age and the comorbid conditions of age, the influenza vaccine is highly cost-effective in reducing influenza-related infections and complications [39,40].

### *Varicella zoster*

Herpes zoster (shingles) is caused by the varicella zoster virus (VZV) and is increasingly prevalent with advancing age, as are its severity and complications [41–47]. The incidence doubles to an annual attack rate of 0.8% from the age of 50 to 80 years [43,44,47]; most cases occur after the age of 60 [41–47]. Two major complications of herpes zoster, postherpetic neuralgia and cranial nerve zoster (often of the ophthalmic nerve, and not infrequently resulting in lower motor neuron paresis), are the most disabling. Postherpetic neuralgia occurs in more than 25% of patients who are at least 60 years old and is strongly associated with sleep disturbance and depression [41,42,46–53]. Bell's palsy [54] and Menier's disease [55], both associated with advanced age, were also linked to herpes zoster. VZV-specific, cell-mediated immunity correlated closely with susceptibility to herpes zoster in large populations, such as patients with lymphomas, bone marrow transplant recipients, and immunocompetent elderly persons [56–69]. It is less clear whether boosting the currently available measures of humoral or cellular immunity to VZV antigens will specifically reduce the risk of developing herpes zoster [61,65–72]; if this is true then herpes zoster will become a vaccine-preventable disease.

### *Human immunodeficiency virus*

HIV infection may be a cause of acquired immunodeficiency in the elderly, and should always be considered part of the differential diagnosis of acquired immunodeficiency in elderly patients with lymphopenia and appropriate risk factors [73–75]. The most common source of AIDS in the elderly is a transfusion [76]. Dementia is often a common presenting feature of AIDS [77]; therefore, AIDS should be considered part of the differential diagnosis of

dementia in aged patients with appropriate risk factors. The possibility that many cases of AIDS go undetected in the elderly has considerable implications for geriatric healthcare workers.

### **Immunesenescence and cancer**

It is commonly believed that immunesenescence is related to the observed increased rate of cancer with advancing age [78]; however, despite the appeal of such an hypothesis, scientific support is limited and the topic remains controversial [79,80]. Profoundly immunodeficient animals or humans are subject to a more frequent occurrence of malignant disease; it stands to reason that others with less severe immunodeficiency would also be subject to more malignancy, perhaps less dramatically so. The malignancies that are associated with profound immunodeficiency (eg, with AIDS or after organ transplantation), however, are usually lymphomas, Kaposi's sarcoma, or leukemia and not the more common malignancies of geriatric populations (lung, breast, colon, and prostate cancers). Accordingly, it is fair to say that the influence of age-acquired immunodeficiency on the incidence of cancer in the elderly is unresolved.

Proponents of an immune explanation point to experiments in which outbred strains of mice with heterogeneous immune functions were followed for their life span [81]. The mice who demonstrated better functions early in life (as determined by a limited panel of assays available at the time on a small sample of blood) had fewer spontaneous malignancies and a longer life than those who were estimated to be less immunologically competent. Recently, a report from Japan in which a cohort of individuals, on whom lymphocyte (specifically NK cell function) measures were obtained decades earlier, demonstrated a reduced incidence of head and neck cancer, a common malignance in the Far East, in those who had better lymphocyte functions [82]. These and other similar observations supported the idea of immune surveillance and indicated the potential importance of immunesenescence in explaining the great increase in incidence of cancer with age.

Despite the controversy regarding the importance of immune surveillance, there is a much greater consensus on the importance of the immunodeficiency of aging in the clinical management of cancer. For example, this immune impairment contributes to the common occurrence of opportunistic infections in older cancer patients.

### **Immune reconstitution**

Numerous interventions have been used in an attempt to enhance immune function in old age (Table 1). Thymic hormones, other hormones, mediations, and cytokines have been proposed as immunoenhancing agents, but none of these has gained clinical acceptance [83,84]. In animals, calorie restriction without undernutrition clearly prolongs life and is associated with immune competence

Table 1  
Methods of immune reconstitution

	Laboratory animals	Clinical studies
Selective		
Interleukin-2	FE	NT
Vaccines	FE	FE
Intravenous immunoglobulin	NT	NT
Nutritional components (eg, Vitamin E, zinc)	FE	FE
Global		
Organ transplantation (eg, thymus, spleen and bone marrow)	FE	NT
Caloric restriction	FE, LE	NT (trials underway)
Global nutritional supplementation	FE, LE	FE
Exercise	FE	FE

*Abbreviations:* FE, functional enhancement; LE, lifespan extending; NT, not tested.

into late life [85–88], but the benefits of calorie restriction in man remain unknown. Caloric restriction studies in longer-lived species (eg, nonhuman primates [89,90]) have been ongoing for almost a decade; the National Institute on Aging has just initiated support for similar dietary intervention studies in humans [91].

When considering immune reconstitution in the context of advanced age, one needs to identify the causes of the immune deficiency; likely it is more than just immunosenescence. Improving immune function under these circumstances would most effectively be accomplished by correcting the underlying cause (eg, cancer surgery, antibiotic treatment for infection or diabetes management); doing so was shown to improve immune function in humans. Medical science has yet to be able to reverse normal aging; the reconstitution of immune functions that have declined because of aging remains a scientific and clinical challenge. Furthermore, there might be a downside to the reconstitution of a robust immune response in older animals or humans. Some investigators suggested that the normal wear and tear on tissues results in the exposure of new antigens to which autoantibodies develop. The functional quality of these antibodies is marginal and clinical autoimmune disease is uncommon; however, with a more robust immune response, it is possible that autoimmune disease might become more problematic. Additionally, the indolent growth and spread of cancer in older patients was linked to diminished growth and angiogenesis factors, some of which are produced by lymphocytes and monocytes; in a murine model, immunological reconstitution resulted in more aggressive tumor growth [92,93].

In laboratory animals in which comorbidities may be more readily excluded, it is possible to examine reconstitution more precisely. Nearly two decades ago, Thoman and Weigle [94] demonstrated that the exogenous administration of recombinant interleukin-2 successfully reconstituted a number of age-reduced, T-cell functions in mice. Similarly, even earlier experiments by Hirokawa et al [95] used heterochronic thymus or bone marrow transplantation to reconstitute

immune functions. These measures resulted in variable successes but were never shown to extend the life span. From a scientific perspective these approaches are interesting and informative, but such invasive and expensive interventions are very unlikely to reach clinical application in this setting.

Thymic hormone (eg, Thymosin alpha one) was given to mice, other mammalian species, and even to humans under a variety of experimental circumstances [96–99]. The influenza vaccine response, known to be reduced with age, was shown to be enhanced by thymic hormone, although the improvement has yet to be shown of clinical importance.

### **Current efforts to enhance immunity in older populations**

#### *Vaccines*

Vaccinations are critically important in maintaining the health of the elderly in the face of declining immunity, and are effective in preventing pneumococcal and influenza pneumonia and tetanus and reduce mortality from these illnesses [15,100–102]. Although elderly people achieve lower peak titers and more rapid declines of serum antibody levels, most healthy elderly achieve titers that are generally presumed protective [103,104]. The chronically ill, frail elderly, particularly institutionalized, malnourished individuals, may not achieve adequate protective peak antibody titers against pneumococcal pneumonia or influenza when immunized with a single dose of vaccine; supplemental doses may be required [105–108]. Older persons may require revaccination with tetanus toxoid more frequently than every 10 years (as currently recommended) to maintain protective levels of antibodies in the serum [109]. The use of new protein conjugate [110] and immunoconjugate [111] vaccines may improve the response in older people.

#### *Intravenous immunoglobulin*

Although not examined strictly in the context of reconstituting age-reduced, immune function, and not explored in laboratory animals, clinicians have resorted to the passive transfer of antibody (by immunoglobulin infusions) for selected patients with recurrent infections or at risk for such. This approach would likely reduce infectious morbidity and mortality in the nursing home, but the complexities and expense of such an undertaking make it unlikely to be studied in a systematic clinical trial.

#### *Nutritional interventions*

Nutritional interventions have proven to be effective and inexpensive approaches to reverse the increasing immune dysfunction that accompanies aging. Older people represent a population who is at significant risk of malnutrition, which was shown to cause immune dysfunction [112,113]. Malnutrition can be caused by common physical conditions, such as disability, medication-induced

anorexia, restrictive diets, poor dentition, and gastrointestinal diseases that can affect nutritional intake and metabolic demand [114]. Furthermore, cultural and psychosocial issues, such as living alone, religious beliefs, and situational depression may reduce nutrient intake and lead to malnutrition. Although it is unclear whether nutritional factors are causally associated to immune senescence, animal and human studies showed that dietary strategies can be used to reverse the increased immune dysfunction that is seen in the elderly [114–117].

Several studies showed that nutritional support in the form of supplementation can improve clinical outcomes and increase immune function in older people. Because these studies are difficult to perform and require large numbers of subjects to identify significant clinical outcomes, most studies use surrogate markers of immune response (eg, antibody titers, delayed-type hypersensitivity (DTH) responses, lymphocyte functional assays) [116,118,119].

Multivitamin or mineral supplements were used in several study designs, all of which reported that augmentation of at least some of the surrogate markers (eg, cytokine production) [114]. Girodon et al [117] conducted a study in 1997 that involved elderly residents in a long term care facility. The study was a 12-month long, double-blind, randomized, placebo-controlled trial; all subjects received supplements regardless of baseline nutritional status. The participants were given a supplement of retinol,  $\beta$ -carotene, thiamine, riboflavin, niacin, pyridoxine, folate, iron, zinc, copper, selenium, iodine, calcium, magnesium and vitamins B<sub>12</sub>, C, D, and E. During the 1 year of the study, there was an increase in CD4<sup>+</sup> T-cell percentages, natural killer cell activity, mitogenic responses, and IL-2/IL-2 receptor expression in the group that received the supplement. In addition, infectious illness days were reduced from a mean of 48 in the placebo group to 23 in the group that received the supplement ( $P = 0.002$ ) and antibiotic use was lowered from an average of 32 days to 18 days ( $P = 0.004$ ).

More focused nutrient supplementation may also be of value. Because of the lack of a clear benefit and the potential damage that can be caused by the overuse of some vitamins (eg, Vitamin A) [120,121], the high dosage of supplemental vitamins should be discouraged, except for the specific minerals that were proved to be beneficial in clinical trials (see later discussion).

Trace minerals, rather than complete vitamin supplements, may be the key nutritional factor in preventing infection in older adults. When given daily, zinc (20 mg of elemental Zn<sup>++</sup>) plus selenium (100  $\mu$ g) decreased infection rates, regardless of whether they were administered with a vitamin supplement [117]. The mean number of respiratory and urinary tract infections was reduced in both groups of subjects who took trace elements, as compared with those who took placebo or vitamins alone. Other studies of zinc supplementation in the elderly found that several forms and dosages of the mineral resulted in enhanced DTH responses; many studies demonstrated enhanced lymphocyte numbers and NK cell function, but none was able to demonstrate an enhancement of humoral immune responses [117,118,121].

In addition, Vitamin E may boost immune responses in elderly people [119,122–124]. Vitamin E is the most effective antioxidant that is found in the

biological membranes of all cells. Although it is not clear how Vitamin E improves immune responses, several studies suggested that it may do so by altering cytokine generation from T cells or macrophages [125,126]. Data on the immune effect of doses less than 200 mg/day are inconsistent [127,128]. Daily supplementation of 200 mg/day or 800 mg/day of Vitamin E in healthy older adults improved DTH responses and increased primary immunization responses to hepatitis B, a T cell-dependent antigen [119,123,124]. In those studies, a dosage of 800 mg/day was not of greater benefit than 200 mg/day [119].

Thus, there is a significant literature body that suggests that a multivitamin or trace mineral supplement taken daily is favorable for the prevention of infection and may decrease antibiotic use in healthy, elderly adults. The supplement should include zinc (elemental zinc >20mg/day) and selenium (100 µg), with additional Vitamin E to achieve a daily dosage of 200 mg/day.

### *Exercise*

Currently there is an increased interest in exercise to enhance health at all ages, including the elderly. Data on preventative or restorative exercise therapy are often conflicting; more research is needed to determine the type, intensity, and total quantity of exercise training that is needed to optimize or potentially restore immune function in the elderly. Exercise is known to significantly alter immune function in all individuals [129], but less is known about the precise interaction between exercise and the aging immune system.

Major considerations for restorative or preventative exercise therapy include the necessary intensity, duration, and onset of an aerobic or resistance training regimen. In elderly patients, it is important to consider whether moderate to strenuous exercise is deleterious to the cellular immune system. Although moderate aerobic activity was shown to be beneficial [130], strenuous exertion actually decreases concentrations of lymphocytes and impairs cellular-mediated immunity [131]. This phenomenon is described by the “Inverted J” hypothesis [130]. Immune function increases with a greater intensity of exercise, until a particular threshold at which immune function begins to decline, forming a visual inverted “J.”

Although it is clear that moderate aerobic exercise is therapeutically more viable for immune augmentation, the data do not completely describe the alternate effectiveness of acute, chronic, or long-term exercise. Cross-sectional studies that compared fit elderly individuals to sedentary controls revealed greater basal NK cell and T-lymphocyte function, as well as accelerated phytohemagglutinin (PHA)-induced lymphocyte proliferation, in the fit individuals [132–135]. Circulating leukocyte and lymphocyte subset counts, however, were similar to those from age- and sex-matched controls [133,134]. The meaningful interpretation of cross-sectional studies is limited to a comparison of sedentary individuals with those who have attained fitness throughout an active lifestyle. This limits the discussion to pre-existing fitness levels, and ignores other critical determinants of senescent immune function such as nutrition, lifestyle, and genetics.

Randomized trials investigated the effect that acute bouts of exercise have on immunity in the elderly. Although a few of these studies showed an increase in immune parameters following a short-term, aerobic training regimen (typically 12 to 24 weeks) [136–138], most comparable studies illustrated little or no immune response to the regimen [132,139]. This discrepancy may be caused by the short-term nature of the training, or a failure to record the most exercise-responsive immune parameters. Typical improvements in immune function were defined by high percent changes in *in vitro* T-cell proliferation to Con A and PHA [137], increased NK tumor cytotoxicity in peripheral blood lymphocytes [136,138], and alteration of levels of pro- and anti-inflammatory cytokines [140].

Although the research is conflicting, several conclusions can be drawn from current literature. Physical training programs commencing after the onset of immune dysregulation do not result in major restoration of the senescent immune system; strenuous programs can actually cause further immune deterioration. It is clear that well-conditioned, elderly humans possess a better-preserved immune system. Whether this is related solely to consistent physical training throughout the lifespan, or to a combination of other lifestyle-dependent factors has yet to be determined.

## Summary

Immune functions decline with age; immunorestorative approaches have been explored in laboratory animals and humans with definite, but limited success. In the clinical setting, the age-associated immune deficiency (immunesenescence) is compounded by the presence of comorbidities that are associated with a functional decline in immunity. Thus, any successful immune reconstitution strategy for humans must involve treatment of the underlying diseases. Furthermore, general health measures such as nutrition and exercises may have powerful effects on restoring immunity, to the extent that malnutrition and a sedentary lifestyle have contributed to existing immune deficiency. More selective approaches, such as with specific cytokines or organ transplantation are of experimental interest but are quite distant from achieving clinical applicability as interventions to restore immunity in the frail elderly.

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