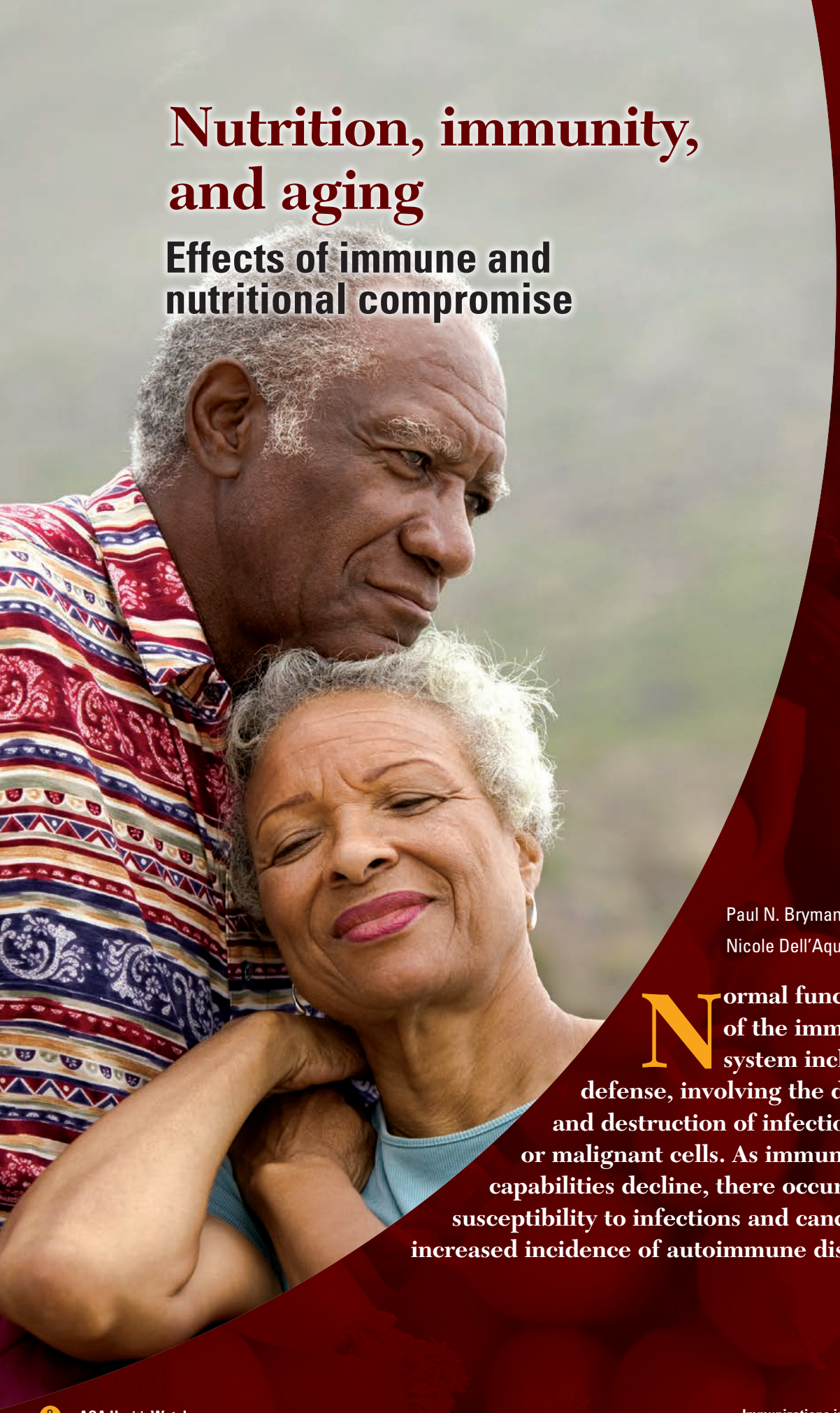
Nutrition, immunity, and aging

Effects of immune and nutritional compromise



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Normal functions of the immune system include host defense, involving the detection and destruction of infectious agents or malignant cells. As immune system capabilities decline, there occurs increased susceptibility to infections and cancer, and an increased incidence of autoimmune disorders.

Nutritional compromise is common in the frail older adult with chronic medical problems; this compromise in nutritional status directly contributes to immune compromise. The effect of these changes in nutritional and immunity status on health maintenance and vaccination needs of older adults is poorly understood and is an area of active research.

Immunosenescence

Immunosenescence refers to the changes that occur in the immune system with increasing age. The clinical consequences of immunosenescence include an increased risk of infections, malignancy, and autoimmune disorders. Aging affects both innate and adaptive immunity, although innate immune mechanisms are better preserved overall.[1]

One of the most prominent features of immunosenescence is the involution of the thymus gland. T cells are generated from precursors that leave the bone marrow and migrate to the thymus for maturation. The thymus gland is most active early in life, reaching its maximum size within the first year of life. The thymus gland then undergoes a steady decline with age. The functional thymic structures are progressively replaced by fatty tissue. These changes are almost complete between the ages of 40 and 50 years. As a result of thymic involution, the number of T cells exiting the thymus progressively decreases with age.[2]

Aging is characterized by an overall decline in T-cell function, as evidenced by a decline in T-cell number, diversity, as well as reduced expansion, differentiation, and signaling intensity. T-cell receptor diversity decreases dramatically after age 65 years, with significantly reduced function. T-cell diversity is critical for protection against new infections, especially viral infections. As a consequence, the ability to mount an immune response against new antigens (ie, infections) declines with age. One dramatic illustration of T-cell decline with age was apparent in a study of 44 centenarians in which T-cell receptors were undetectable in 84% of the participants.[3] Loss of T-cell function is considered to be among the primary reasons older adults are more vulnerable to infectious diseases.

Memory B and T cells

The generation of long-lasting protective immunity is one of the most important characteristics of the adaptive immune system. Immune memory is essential in allowing individuals to defend themselves from infections to which they have previously been exposed. As the thymic output declines, aging adults rely more on reexpansion of experienced memory cells for defense against recurrent infections. Immune responses to recall challenge appear to be relatively well preserved with aging.

An example of this phenomenon was seen during the 2009 H1N1 influenza pandemic, in which older adults were better protected from H1N1 infection than middle-aged adults, probably in response to an H1N1 virus that circulated prior to 1957. The antibody memory for 2009 H1 was higher in the older-aged adults than in the middle-aged adults.[4] Conversely, animal studies suggest that T-cell memory generated for the first time in old animals is defective because of age-related defects in response to antigenic stimulation that are caused, in part, by decreased function of CD4 T cells.[5]

Effect of malnutrition

Adequate nutrition is vital to healthy aging. Malnutrition is very common in older adults and is associated with increased morbidity and mortality.[6] In a Swedish study, malnutrition was present in 60% to 80% of patients aged older than 60 years admitted to the hospital.[7] In general, energy requirements decrease with age as a consequence of a decline in lean body mass and decreased physical activity. Despite this, older adults are at risk for malnutrition because of any of the following: dental or swallowing problems that might interfere with eating; loss of smell or taste sensations; chronic illnesses that interfere with digestion or absorption of food; increased nutritional requirements; medication side effects; depression and social isolation; functional, visual, and cognitive impairments; and economic barriers.

Malnutrition is associated with adverse clinical outcomes, including increased risk of morbidity and mortality. Other complications include increased hospital length of stay, poor wound healing, increased susceptibility to infection, increased dependence on others for assistance with activities of daily living, and poor outcomes of other underlying chronic disease processes. Malnutrition is defined, simply, as a

state of being poorly nourished and is most commonly associated with being undernourished (lacking nutrients). Obese individuals also can be classified as malnourished, resulting from the consumption of excessive nutrients that are of little nutritional value. Malnutrition should not be considered a normal part of the aging process, but many of the expected changes seen in older adults are known to increase their risk for global malnutrition (reduced intake or increased demand for nutrients), the most common type of malnutrition in this age group.[8]

Malnutrition is associated with immune defects, in particular a decrease in T-cell function. So, older adults with malnutrition have both age and malnutrition adversely affecting T-cell function. Malnutrition also is associated with an increased risk for and adverse outcomes from infections. Deficiencies of vitamins A and E, vitamin C, vitamin B_{12}, and folate, vitamin B_6, vitamin D, as well as zinc, selenium, magnesium, and copper, have been noted in older adults, although the precise effects of these deficiencies on immune function are not well defined.[9-11]

Immunosenescence increases susceptibility to infection and reduces effectiveness of vaccination.

Vaccine recommendations

Recommendations have been issued for routine vaccination of healthy older adults (*Table*). Vaccines to protect against tetanus, influenza, pneumococcal infections, and zoster are particularly relevant to individuals aged older than 65 years.

Use of higher-dose (HD) vaccines

Increasing the dose of certain vaccines may improve effectiveness in older adults. Results of a study of patients with asthma suggested that those aged 60 years and older produced adequate levels of seroprotective antibody to H1N1 vaccine in response to a 30-µg dose, but not to a 15-µg dose. In response to this and other studies indicating that the conventional vaccine produced marginal protection in older adults, the US Food and Drug Administration approved a seasonal flu vaccine for the 2010 fall flu season that was specifically designed for people aged 65 years and older. This preparation, Fluzone High-Dose, contains 4 times as much of the active antigen component as a conventional flu shot, resulting in a stronger antibody response in older adults. There was a statistically significant increase in the level of antibody response induced by HD influenza vaccine, compared with that induced by standard-dose vaccine, without an attendant increase in the rate of adverse reactions.[12]

Vaccine boosters also can be effective

In a study evaluating preimmunization and postimmunization titers for the tetanus, diphtheria, pertussis, and polio vaccines in 252 older individuals compared with a group of younger adults, protective titers were lower for the inactivated vaccines compared with those for the live polio vaccine. For the inactivated vaccines, postimmunization titers were significantly higher in patients with higher preimmunization titers, indicating that routine booster programs for these vaccines could help achieve better protection in older adults.[13]

Nutritional status

In addition to pathogen load, nutritional status is a major factor influencing T-cell responses. Even healthy older subjects who live at home often experience subclinical protein-energy malnutrition (PEM) and/or micronutrient deficiency; it is worth noting that PEM is much more common among nursing home residents. PEM is associated with a decrease in immunity and an increase in the occurrence of infectious diseases, both of which are exacerbated in older adults.[14]

The effects of PEM on T-cell function in younger people are almost identical to those observed in healthy older individuals, namely, a decrease in delayed-type hypersensitivity, interleukin-2 production, T-cell proliferation, and antibody responses.[15] Future researchers should examine the effects of refeeding before infection on the immune response and the response to primary viral infection.[14]

Failure to thrive

"Failure to thrive" is a term that initially appeared in the pediatric literature. Regarding the geriatric population, it is used to describe a gradual decline in physical and cognitive function, usually accompanied by weight loss

Table. Recommendations for Routine Vaccination of Healthy Older Adults

Vaccine	Age Group (years) 19-21	22-26	27-49	50-59	60-64	>65
Influenza	1 dose annually					
Tetanus, diphtheria, pertussis (Td/Tdap)	Substitute 1-time dose of Tdap for Td booster; then boost with TD every 10 years					
Varicella	2 doses					
Human Papillomavirus (HPV), female	3 doses					
Human Papillomavirus (HPV), male	3 doses	3 doses				
Zoster					1 dose	1 dose
Measles, mumps, rubella (MMR)	1 or 2 doses					
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses					1 dose
Pneumococcal 13-valent conjugate (PCV13)	1 dose					
Meningococcal	1 or more doses					
Hepatitis A	2 doses					
Hepatitis B	3 doses					

For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection; zoster vaccine recommended regardless of prior episode of zoster

Recommended if some other risk factor is present (eg, on the basis of medical, occupational, lifestyle, or other indication)

No recommendation

Source: ACIP Adult Immunization Work Group, Bridges CB, Woods L, Coyne-Beasley T; Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for adults aged 19 years and older—United States, 2013. *MMWR Surveill Summ.* 2013;62(suppl 1):9-19.

and social withdrawal that occurs without immediate explanation.

Failure to thrive in the older adult is characterized by weight loss greater than 5% of baseline, decreased appetite, poor nutrition, and inactivity, often accompanied by dehydration, depressive symptoms, impaired immune function, and low cholesterol levels.

Failure to thrive also is not considered a normal part of aging. Four syndromes seen in patients with failure to thrive are impaired physical function, malnutrition, depression, and cognitive impairment. Assessments of patients suspected of failure to thrive should include information on physical and psychological health, functional ability, socio-environmental factors, and nutrition.[16]

Potential interventions

There are no specific therapies that have demonstrated convincingly that they counter normal immunosenescence. Still, adequate nutrition is likely essential for optimizing immune function, and there are some data indicating that regular, moderate exercise, working synergistically with nutritional support, also is important.[17]

Studies demonstrating that vitamin or mineral supplements can boost immune function are lacking. Available data do indicate that vitamins (A, D, E, B_6, B_{12}, folate, and C) and trace elements (selenium, zinc, copper, and iron) are necessary for normal immune function. In addition, the prevalence of certain nutritional deficiencies in the geriatric population (eg, vitamins D and B_{12}) is sufficiently high that certain supplements are indicated. Beyond achieving the recommended daily amounts of nutrients, however, there are no data to suggest that further supplementation can improve immune function.

Few studies have evaluated the effect of dietary practices on specific immune functions. Results of 1 study suggested that fruit and vegetable consumption improved antipneumococcal antibody response in subjects aged 65 to 85 years, although there were technical issues with the measurement of immune response, and so more work is needed in this area.[18] The study showed that increased fruit and vegetable consumption improves the Pneumovax II vaccination antibody response in older people, thus linking an achievable dietary goal with improved immune function. In a 16-week randomized-controlled trial, the study examined the effects of fruit and vegetable consumption on immune function in older adults. Two groups were selected randomly—1 group consumed 5 portions per day of a wide variety of fruits and vegetables daily; the other, the control group, consumed 2 or fewer portions of fruits and vegetables daily.

Participants were interviewed for dietary history and provided blood samples at set intervals throughout the study. At the 12-week interval, participants received both the tetanus toxoid and the Pneumovax II vaccine. At the end of the 16-week trial, participants provided a blood sample to measure nutritional status and immune function. The trial concluded that there was no difference in antibody binding to tetanus toxoid between the 2 groups, but that antibody bonding to pneumococcal capsular polysaccharide was higher in the group who consumed 5 portions per day of fruits and vegetables vs the control low-intake group. The results were limited to those who had never received the Pneumovax II vaccine, indicating that the greatest response was seen in naïve B cells vs memory B cells.[18]

Multivitamin and mineral supplementation has been shown to provide benefit for the prevention of clinical events in older patients. Two separate studies reviewed both community-dwelling older adults and institutionalized long-term care patients and the outcomes of oral vitamin and mineral supplementation on infections in older subjects.[19] The trial investigating healthy community-dwelling older participants provided a customized supplement containing retinol, β-carotene, thiamine, riboflavin, niacin, pyridoxine, folate, iron, zinc, copper, selenium, iodine, calcium, magnesium, and vitamins B_{12}, C, D, and E. The study concluded that infectious "illness days" were reduced from 48 to 23 days and antibiotic days were reduced from 32 to 18 days in placebo participants vs those receiving the customized supplement. The second trial studying institutionalized older adults suggested that trace minerals, rather than vitamins, constitute a key nutritional factor for preventing infection in older adults. The combination of both elemental zinc (20 mg) and selenium (100 µg), given daily with or without additional vitamin supplementation, decreased rates of infection and improved responses to influenza vaccine.[19]

Final notes

As stated previously, there are at present no specific therapies that have demonstrated convincingly that they counter normal immunosenescence in the aging population. However, adequate nutrition is important, and there may be a role for regular, moderate exercise. In addition, research regarding how older adults respond to vaccination has resulted in several changes in vaccination guidelines and several potential strategies for creating vaccine preparations that are more effective in this age group. Further research in this area will be increasingly important as the aging population increases worldwide. HW

References

1. Weiskopf D, Weinberger B, Grubeck-Loebenstein B. The aging of the immune system. *Transpl Int*. 2009;22(11):1041-1050.
2. Naylor K, Li G, Vallejo AN, et al. The influence of age on T cell generation and TCR diversity. *J Immunol*. 2005;174(11)7446-7452.
3. Nasi M, Troiano L, Lugli E, et al. Thymic output and functionality of the IL-7/IL-7 receptor system in centenarians; implications for the neolymphogenesis at the limit of human life. *Aging Cell*. 2006;5(2):167.
4. Hancock K, Veguilla V, Lu X, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med*. 2009;361(20);1945.
5. Haynes L, Eaton SM, Burns EM, Randall TD, Swain SL. Newly generated CD4 T cells in aged animals do not exhibit age-related defects in response to antigen. *J Exp Med*. 2005;201(6):845-851.
6. Drey M, Kaiser MJ. Malnutrition in the elderly [in German]. *Dtsch Med Wochenschr*. 2011;136(5):176-178.
7. Persson MD, Brismar KE, Katzarski KS, Nordström J, Cederholm TE. Nutritional status using mini nutritional assessment and subjective global assessment predict mortality in geriatric patients. *J Am Geriatr Soc*. 2002;50(12):1996-2002.
8. Hickson M. Malnutrition and ageing. *Postgrad Med J*. 2006;82(963):2-8.
9. Kawakami K, Kadota J, Iida K, Shirai R, Abe K, Kohno S. Reduced immune function and malnutrition in the elderly. *Tohoku J Exp Med*. 1999;187(2):157-171.
10. Chandra RK. Nutrition and the immune system from birth to old age. *Eur J Clin Nutr*. 2002;56 suppl 3:S73-S76.
11. Cunha DF, Cunha SF, Unamuno MR, Vannucchi H. Serum levels assessment of vitamin A, E, C, B2 and carotenoids in malnourished and non-malnourished hospitalized elderly patients. *Clin Nutr*. 2001;20(2):167-170.
12. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GF. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis*. 2009;200(2):172-180.
13. Kaml M, Weiskirchner I, Keller M, et al. Booster vaccination in the elderly: their success depends on the vaccine type applied earlier in life as well as on pre-vaccination antibody titers. *Vaccine*. 2006;24(47):6808-6811.
14. Ritz BW, Gardner EM. Malnutrition and energy restriction differentially affect viral immunity. *J Nutr*. 2006;136(5):1141-1144.
15. Fulop T, Pawelec G, Castle S, Loeb M. Immunosenescence and vaccination in nursing home residents. *Clin Infect Dis*. 2009;48 4):443-448.
16. Robertson RG, Montagnini M. Geriatric failure to thrive. *Am Fam Physician*. 2004;70(2):343-350.
17. Kohut ML, Arntson BA, Lee W, et al. Moderate exercise improves antibody response to influenza immunization in older adults. *Vaccine*. 2004;22(17-18):2298-2306.
18. Gibson A, Edgar JD, Neville CE, et al. Effect of fruit and vegetable consumption on immune function in older people: a randomized controlled trial. *Am J Clin Nutr*. 2012;96(6): 1429-1436.
19. High K. Nutritional strategies to boost immunity and prevent infections in elderly individuals. *Clin Infect Dis*. 2001;33(11):1892-1900.

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