INTRODUCTION

One of the successes of medical science is the increase in life expectancy of mankind. As life expectancy has increased, there is longer exposure to intrinsic and extrinsic insults. Older people suffer frequently from severe community-acquired and nosocomial infections than younger people, and tend to experience poorer outcomes. Latent intracellular pathogens such as viruses (e.g. Herpes), bacteria (e.g. Mycobacteria) or fungi (e.g. Candida) reactivate and opportunistic infections manifest themselves at increased rates in old age. Increased susceptibility to infection reflects the profound age related changes which the immune system undergoes and which are collectively termed immunosenescence. Clarifying the basic mechanisms of age related immune dysfunctions and understanding the exact nature of underlying defects enables us to take measures that contribute to healthy ageing.

BASICS OF IMMUNITY

In this section a brief review of the immune system is provided for recollection. Immunity is the state of protection, against any substance that is recognized as foreign by the body. The immune system is composed of two major subdivisions, the innate or nonspecific immune system and the acquired or specific immune system. The innate immune system is a primary defence mechanism against invading organisms, while the adaptive immune system acts as a second line of defence. Both aspects of the immune system have cellular and humoral components by which they carry out their protective functions. In addition, there is interplay between these two systems, i.e., cells or components of the innate immune system influence the adaptive immune system and vice versa.

Innate Immunity- Innate or nonspecific immunity involves barriers that keep harmful materials from entering the body. It is a key element of the immune response including several cellular components such as macrophages, natural killer (NK) cells, and neutrophils, which provide rapid first-line defence against pathogens.

Acquired Immunity- Acquired immunity is immunity that develops with exposure to various antigens, specific to that antigen.

Active Immunity- The ability of an organism to resist disease, either through the activities of specialized blood cells or antibodies produced by them in response to natural exposure. Passive Immunity- Passive immunity is due to antibodies that are produced in one’s body and transferred into the others or may also be due to injection of antiserum (antibody). It provides immediate protection against an antigen, but does not provide long-lasting protection. Cell-mediated Immunity- It is the type of immunity that functions in defence against fungi, parasites, bacteria, and viruses inside host system and against tissue transplants, with highly specialized cells that circulate in the blood and available in local tissue site.

Humoral Immunity- This is the component of the immune system that involves antibodies secreted by B cells and circulate as soluble proteins in blood. Cells in the Immune System

All cells of the immune system originate from a hematopoietic stem cell in the bone marrow, which gives rise to two major lineages, a myeloid and a lymphoid progenitor cell (Figure 2). These progenitor cells subsequently give rise to the myeloid cells (monocytes, macrophages, dendritic cells,
Changes in the immune system with age

Innate immunity: Although the production of macrophages, NK cells, and neutrophils increases with age, but elderly macrophages have a reduced ability to secrete tumour necrosis factor (TNF), essential for the secretion of other cytokines critical for bone marrow stromal integrity, such as IL-6, IL-11, monocyte colony stimulating factor (M-CSF), granulocyte-macrophage (GM)-CSF and receptor activators of NF-κB ligand. Ageing also dampens the secretion of IL-7, an essential survival cytokine for developing lymphocytes. Furthermore, pattern-recognition receptors such as the TLRs, expression and function decline with age, resulting in the decreased production of pro-inflammatory cytokines and chemokines. As a result, the immune response and vaccine effectiveness in older persons appear to be impaired IL-2 responsiveness. Age related reductions in NK-cell-mediated cytotoxic activity appear to be clinically relevant as they are associated with an increased risk of infection and death in elderly subjects. Furthermore, long-lived cells dominate within their NK cell population. Certain viral infections also affect NK cells differently from what observed in the young.

Adaptive immune system: The competency of the adaptive immune function decreases with age, primarily because of the decline in production of naive lymphocytes in the bone marrow and thymus as well as the expansion of incompetent memory lymphocytes.

Changes in cytokines with age: Cytokines are diverse and potent chemical messengers secreted by the cells of the immune system—and the chief tool of T cells. Lymphocytes, including both T cells and B cells, secrete lymphokines, while monocytes and macrophages secrete monokines. Cytokines encourage cell growth, promote cell activation, direct cellular traffic, and destroy target cells—including cancer cells.

Ageing can induce altered representation and function of regulatory T cell subsets (NKT and Treg cells) and impair the protective T cell response against the pathogen and disrupts the disease pathology, thus facilitates faster progression and development of severe forms of diseases in aged individual infected with any pathogen.

Changes in humoral immunity: Due to the complex network of cellular interactions and the multi factorial process of aging, numerous impairments in humoral immunity have been reported. Changes in the quality of the antibody response with age include shifts in antibody specificities from foreign to autoantigens, in antibody isotypes from IgG to IgM, in antibody affinities from high to low and in the antibody idiotypic repertoire. These changes can be traced to an impaired capacity of T cells to facilitate: (a) the maturation of B cells in respect to isotype and affinity maturation in the periphery and (b) the development of a diverse B-cell repertoire from precursors within the bone marrow. Age-associated T-cell impairments appear to be the basis for the shift from adaptive to natural humoral immunity.

Changes in cellular immunity: Much of the decrease in immune-responsiveness seen in elderly populations is associated with changes in T cell responses. The loss of effective immune responsiveness is largely due to alterations within the T cell compartment which occur, in part, as a result of thymic involution. One of the most consistent changes noted in T cells with advancing age is the decrease in the proportion of naive T cells with a concomitant increase in T cells with an activated/memory phenotype. In addition, there is evidence that the T cell population from aged individuals is hyporesponsive. Naive CD4+ T cells display decreased T cell receptor stimulation and altered profiles of cytokine secretion. In parallel, the helper function of naive CD4+ T cells for antibody production by B cells is also decreased. Studies have reported defects in the early events of the TCR signalling cascade with aging in humans.

Fig. 1: Schematic presentation of the immune system

Fig. 2: Origin of cells in the immune system
some evidence that the signalling of IL-2 and IL-6 receptors is altered in human T cells, mainly in relation to the JAK/STAT pathway. The most widely acknowledged phenotypic change observed in T cells during aging is the loss of CD28. The absolute number of peripheral blood lymphocytes (PBL) also decreases with aging.

Increase of immature T cells CD2+ CD3− is an ageing phenomenon related to T-cell declining proliferation. Recently it was shown that increase of immature T cells was due to an increase in different subtypes of the CD2+ CD3− population, double-negative CD2+ CD4− CD8− and double-positive CD2+ CD4+ CD8− subpopulations, the former being associated with nutritional deficit, the latter with associated diseases. 6,7

PROBABLE CAUSES OF IMMUNE SENESCENCE

Though ageing is partially genetically predetermined, external factors also affect immune senescence. Immune system in the elderly is the result of a continuous remodelling process. 8 Major epigenetic mechanisms include DNA methylation, histone modifications, structural modifications of the chromatin etc. Furthermore, an increased pace of telomere shortening is believed to be a major factor of accelerated ageing and immune senescence. 9 Socio-demographic factors like residency, institutionalisation, income, education, life style and disability in daily living contribute to immune senescence. Unhealthy habits (smoking, alcoholism), co-morbidities such as chronic obstructive pulmonary diseases, heart failure, diabetes mellitus, rheumatic and autoimmune diseases and long term treatments with corticosteroids, as well as severe cognitive impairment, Alzheimer disease and medications also contribute to declining immune activity. Malnutrition, a very important issue in Indian context, has negative impact on immunity. 4

CLINICAL IMPLICATION OF IMMUNE SENESCENCE

Pneumonia and influenza are among the top ten causes of death in individuals aged 65 and older. Nosocomial infections are also significantly increased in elderly individuals. This could be the result of decreased immunologic function, in addition to a decreased efficacy of vaccines in the elderly. However, there are several other factors that are likely to contribute to increased infections in elderly individuals: malnutrition, co-morbid conditions (diabetes, chronic obstructive pulmonary disease), diminished mucosal barriers, decreased cough reflex, and mechanical changes to the urinary tract system are among others.

The clinical presentation of infections in older patients may be different from that in younger patients due to decrease ability to mount inflammatory cytokine responses in the face of infection. Cancer also increases dramatically with ageing. They exhibit larger and more aggressive tumours. 6,7 Probable explanation may be enhanced cancer specific inflammatory response, genetic polymorphism, distinct expression levels of IL-6 and IL-10 could affect tumour incidence and progression. Additionally limited pool of naïve T cell and impaired processing may contribute to decreased recognition of emerging tumour antigen and increased incidence of tumours. More over tumours often express Fas ligand, which induces apoptosis of T cells through Fas receptor. With ageing Fas receptor is elevated, thereby allowing tumour growth.

IMMUNOLOGICAL INTERVENTION

Vaccination is the only available documented strategy to augment (partially) immune system of elderly people to reduce the morbidity and mortality related to infection.

Influenza vaccine- It is a trivalent inactivated vaccines-TIV (newly approved with higher dose), should be given to all Geriatric patient every year before the Flu season starts. As influenza mutation is rapid due to antigenic shift and drift, protection has to given every year and composition of vaccine also changes. It reduces the likelihood of hospitalization for influenza related vascular event (MI or CVA) or pneumonia, each by about 30%. Immune responses to TIVs Tend to be lower in the oldest old, but still provide important, cost effective approach to influenza prevention

Side effects- Adverse effects are usually mild and include injection site inflammation and soreness, sometimes systemic symptoms like cough, fever, aches. Very rarely life-threatening allergic reactions may occur and 1 in 1 million people vaccinated may develop Guillain-Barre Syndrome (GBS). Pneumococcal vaccine- It is a 23 valent pneumococcal polysaccharide vaccine (PPSV23) and has an average protective efficacy about 60%-70% against invasive pneumococcal disease in immune competent older people. Single dose polyvalent injection should be given to all 65 years or above, who have not received before. A second dose of PPSV23 is recommended 5 years after the first dose for persons aged 19—64 years with functional or anatomic asplenia and for persons with immune-compromised state (haematological malignancy, chronic renal failure, HIV, congenital or acquired immunodeficiency, diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids or radiation therapy and Solid organ transplantation). Though response to vaccine in oldest old is variable and efficacy is less than young old, due to weaning humoral and cellular immunity, multiple boosters to augment the immune status could be an option. But conclusive multi-centric trials are lacking.

Side effects- About half of the recipient develops redness or pain at injection site. Less than 1 percent develops a fever, muscle aches, or more severe local reactions. 12

Herpes zoster vaccine - The availability of a safe and effective vaccine for zoster offers an opportunity to decrease the burden
of this disease and its complications especially post-herpetic neuralgia with severe pain, among persons with high risk group mainly frail elderly. FDA recommends Zostavax (live vaccine) for use in people of 60 years or above to prevent shingles regardless of whether they had suffered from chickenpox/shingles or not. This is a one-time vaccination. There is no maximum age limit for getting the shingles vaccine. Vaccine reduces the incidence of shingles by approx 51.3% and post herpetic neuralgia and pain by 66.5%. Although effective antiviral medications are available, many patients might not get early diagnosis and treatment.

Side effects- Herpes zoster vaccine is a very safe but few may develop a chickenpox-like rash near the place where they were vaccinated. As a precaution, this rash should be covered until it disappears.

Contraindication- Herpes zoster vaccine should not be administered in patient with active shingles or post-herpetic neuralgia. As it is a live vaccine, it not recommended in patients with HTV/ATDS or other disease that affects the immune system, patients on long term steroid therapy, patients with haematological malignancy and patients receiving chemo or radiotherapy.

**NUTRITIONAL INTERVENTION**

Some vitamins and mineral supplementation can be of help in augmenting immunity, for example vitamin A contributes to the maintenance of epithelial integrity in the respiratory and gastrointestinal tracts, thereby reduces the risk of influenza infection, vitamin D enhances activation of Toll-like receptors (TLRs) and increases cathelicide production, which contributes to the destruction of intracellular organism. Zinc has a role in helping phagocytosis, and maintenance of the complement cascade. While malnutrition has detrimental effect on immunity, calorie restriction has positive effect on T cell function. So a balanced approach would be justified.4,11

**EXERCISE AND LIFESTYLE MODIFICATION**

Moderate exercise employed for the elderly to maintain their physical functions and cardiovascular fitness improves the T helper immune responses. Smoking and alcohol consumption should be stopped and lipid profile should be within normal range to maintain a healthy immune system.

**CONCLUSIONS**

Immune senescence is a major challenge against active ageing. It has direct effect on development of frequent and severe infection, which further increases morbidity, dependence and death in elderly population. Overwhelming detrimental effect of weaning immunity precipitates aggressive malignancy in them. Vaccination is an effective measure but efficacy reduces with extreme ageing, which mandates discovery of new and augmented vaccination strategy. Telomerase based approach and gene therapy could be future prospects.

**REFERENCES**

1. Fig.1 http://futuresurgeon0607.blogspot.com/
2. Fig.2 http://www.textbookofbacteriology.net/innate.html

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**Table 1: Components, functions and ageing of innate immune system**

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<thead>
<tr>
<th>Component</th>
<th>Function</th>
<th>Ageing changes</th>
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<tbody>
<tr>
<td>Epithelial barriers</td>
<td>Prevention of microbial entry</td>
<td>Impaired</td>
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<tr>
<td>Mannose-binding lectin</td>
<td>Opsonization and killing of microbes</td>
<td>Impaired</td>
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<tr>
<td>Cytokines and chemokines</td>
<td>Inflammation, activation of macrophages, stimulation of INF-gamma</td>
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<tr>
<td>NK cells</td>
<td>Killing of infected cells and tumour cells</td>
<td>Production of pro-inflammatory cytokotoxic and chemokines decreases</td>
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<tr>
<td>Neutrophils</td>
<td>Phagocytosis, killing of pathogens</td>
<td>Decreases MHC class I expression, oxidative burst</td>
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<tr>
<td>Complement</td>
<td>Opsonization of microbes, killing of microbes</td>
<td>Impaired</td>
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