UNIT 3 INFECTION AND IMMUNITY

Structure

3.0 OBJECTIVES

After reading this unit, you should be able to:

- describe the normal immune mechanisms;
- enumerate age related changes in the immune mechanisms;
- discuss pathogenesis of infection in old age;
- list common infections in old age;
- discuss general principles of antibiotic therapy in old age and immunizations in old age; and
- outline the approach to older patients with an infectious disease.

3.1 INTRODUCTION

Immune system has an important role in sustenance of life in all complex forms of living beings. Resistance to invasion of parasitic microbes and surveillance against autonomous cell growth are important functions of the immune system. Aberrant functioning of the immune system or autoimmunity can also cause disease. With aging there is a gradual alteration in the structure and function of the immune system which starts with involution of thymus in puberty.

As has been discussed in the Unit 1, Block 2 of Course 1, we know that with aging several structural changes occur in most organ systems in the human body. These changes along with decline in immunity can lead to invasions of various organs by microbes. However because of

altered physiological reserves, response to invasion by pathogenic micro-organisms may be different clinically in the older patient.

In this unit, you will be learning about alterations in the immune system, pathogenesis, clinical presentation and management of infectious diseases in old age. You will also learn principles of antibiotic therapy and immunization against infectious diseases in older people

3.2 BASIC CONCEPTS

The immune system protects us from pathogens such as viruses, bacteria, fungi, protozoa and multi-cellular parasites. You must have learnt immunology in great detail during your undergraduate years. In the next few paragraphs we shall revise some concepts in immunology to understand this unit better.

3.2.1 Physical and Chemical Barriers

Our environment contains a great variety of micro-organisms, which can parasitize us for their survival and cause disease in us. However, there are several physical and chemical barriers in our body to microbial invasion. As a result only a few organism gain entry. These barriers include:

- intact skin and fatty acids in it
- acidic pH of stomach and female genital tract
- lysosomes in tears and other body secretions
- mucous and cilia of upper and lower respiratory tract
- flushing of urinary tract with urine
- commensals over skin and mucous membrane.

3.2.2 Innate and Adaptive Immunity

A small number of organisms however cross these barriers. Protection against these organisms is mediated through the immune system. The immune system recognizes the pathogen as a foreign material and mounts a reaction to eliminate it. This immune response can be of two types—innate (non-adaptive) and adaptive.

Innate Immunity

Innate or non-adaptive immunity is non-specific in nature and is not altered by or related to exposure to the organism.

Adaptive Immunity

Adaptive immunity on the other hand is specific and is related to exposure to the organism and improves with each successive exposure to the organism. Adaptive immunity may be life long against certain organisms such as measles virus. There are two key features of adaptive immunity which are: i) specificity i.e. the response is only against a particular organism, and ii) memory i.e. the organism will be remembered for ever by the immune system.

Immune response is mediated by several types of leukocytes. As a rule of thumb, phagocytes (neutrophils, monocytes and macrophages) are mediators of innate immunity where as adaptive immunity is mediated by lymphocytes. However both the systems of immune response are integrated with each other and act in tandem in eliminating the organism.

3.2.3 Immune Response

It is customary to classify immune response into two types: i) humoral immunity, and ii) cell-mediated immunity.

Humoral Immunity

Immune response primarily mediated by B cells and antibodies, is termed as humoral immunity. The primary event in humoral immunity is binding of antibody with the antigen and the secondary event is activation of complement system in absence of which the primary event will be of no significance.

Cell Mediated Immunity

Immune response against organisms and tumour cells in which antibodies have subordinate role is termed as cell mediated immunity. Phagocytosis and T-cell mediated cytotoxicity in conjunction with cytokines are the primary events in cell mediated immunity.

Both these arms of immunity are not exclusive to each other and work in a coordinated manner.

Certain sub-group of T lymphocytes, called T helper cells (TH cells or CD4 cells) have a central role in all types of adaptive or specific immune response. TH cells are of two types TH1, which promote macrophage activation and TH2, which promote antibody production. There is another group of T lymphocytes termed T suppressor cells (CD8 cells), which inhibits T helper cells and keeps the immune response under control.

3.3 AGE RELATED CHANGES IN THE IMMUNE SYSTEM

The immune system undergoes several changes with advancing age. Both humoral and cell mediated immunity are affected by aging. The commonest markers of immunosenescence are involution of thymus and decreased production of specific antibodies following exposure to antigens and vaccines.

The total number of lymphocytes, monocytes, neutrophils and concentration of serum immunoglobulins remain within normal range. Immunosenescence is not exactly a state of immunodeficiency but a state of dysregulation. The age associated changes in the defence mechanisms of different organs are presented in Table 3.1.

3.4 CONSEQUENCES OF IMMUNOSENESCENCE

There are a number of consequences of immunosenescence in old age. These are discussed below:

1) **Autoimmunity**

Antibody response to specific antigenic challenge declines in old age. However, the absolute immunoglobulin levels remain either normal or high. Several autoantibodies, namely, anti-nucleoprotein antibody, anti-IgG antibody, anti-thyroglobulin antibody, rheumatoid factor and anti-vascular antibody etc. are detected frequently in older patients. These autoantibodies are against host antigens with uncertain pathological significance.

Several autoimmune diseases have their highest prevalence during old age, namely, autoimmune thyroiditis, pernicious anaemia, temporal arteritis, bullous pemphigus. However not all autoantibodies detected in old age are diagnostic of disease.

There are suggestions that auto-immunity may have a role in impaired tissue repair and regeneration process and there by accelerate the process of aging.

Table. 3.1: Age Related Alterations in Organ-specific Defences

Organ	Age related change in defence mechanism	Result
Kidney	inability to maintain osmolality, pH; and concentration of organic acid and urea	bacterial colonization, bacteriuria
Ureters	inadequate peristalsis and incompetent vesico-ureteric valve	reflux, ascending infection
Bladder	impaired emptying capacity and defective surface mucin	reflux, ascending infection
Lungs	reduced expiratory flow rate and vital capacity; increased residual volume and ineffective alveolar macrophage function	impaired clearance of infection
Bronchi	sluggish mucociliary transport infection infection	delayed clearance of
Pharynx	abnormal swallowing mechanism and impaired cough reflux	aspiration
GI tract	loss of gastric acidity	bacterial overgrowth
Skin	breach in skin integrity due to epidermal and dermal atrophy and decrease in number and function of Langerhan's cells	increased infection

Though not confirmed, there are reports to suggest that atherosclerosis and coronary artery disease may also be related to autoimmune vascular injury.

2) **Cancer**

Aging is the single most important factor in development of cancer. The natural history of cancer in old age also tends to be different compared to younger subjects, e.g. breast cancer in elderly women have indolent course whereas leukemia tends to run an explosive course.

The role of immunosenescence in higher prevalence and different natural history of cancer in old age is yet to be proven definitively. The proposed role for immuno-senescence in cancer includes reduced surveillance of malignant cells, reduced activity of cytotoxic T cells in eliminating cancer cells; and growth promoting action of circulating autoantibodies.

3) **Infection**

The most profound effect of immunosenescence is higher risk of infection and greater chance of complications and death from infectious disease.

4) **Secondary Causes of Poor Immune Function**

In contrast to normal age related changes in immune system which result in immuno-dysregulation, several other factors may lead to reversible decline in immunity old age, which is severe and life threatening.

Secondary causes of poor immune function in old age include:

Malnutrition: Malnutrition is usually present in more than 50 per cent of the hospitalized elderly, due to socio-economic reasons or chronic illness.

Polypharmacy: Common drugs that cause immunodeficiency are non-steroidal anti-inflammatory drugs, steroids, antibiotics, anti-thyroid drugs, anti-depressants, anti-psychotics,

diuretics, anti-convulsants, H_2-receptor blockers, oral hypoglycemic agents and calcium channel blockers.

Psychosocial Factors: Isolation, depression and stresses of old age are also potential causes of immuno suppression.

HIV Infection: In recent years HIV infection has emerged as an important cause of immunodeficiency in young adults. In older subjects also HIV infection can be a serious health problem with transfusion as the source of HIV infection.

Consequences of Aging and Immune System

1) Aging of the immune system leads to defects in T cell mediated defenses and impairs regulation of B cell response.

2) There is decline in the ability to mount antibody response, impaired macrophage hypersensitivity response and decline in NK cell activity.

3) The ultimate effects of immunosenescence are complex and are modulated by organ specific response.

4) Age associated decline in immune function is mild in magnitude but irreversible.

5) Several other factors also lead to severe but potentially reversible immunodeficiency.

Check Your Progress 1

1) Differentiate between innate and adaptive immunity.

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2) Enumerate the commonly used drugs that cause immunosuppression.

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3.5 INFECTIOUS DISEASES IN OLD AGE: GENERAL CONSIDERATIONS

We have now known that older subjects are at higher risk of suffering from infectious disease in view of their deranged immune status.

Let us look at certain general aspects of infectious disease in old age.

Infectious diseases in old age are significant health problems because:

- Infection is the third commonest cause of hospitalization only after acute myocardial infarction and stroke.
- Infections account for two—pneumonia and tuberculosis—of the top five causes of death in rural India.
- Infections come as the terminal event in most neurodegenerative diseases and chronic heart failure.
- Fifty per cent of elderly subject suffer from at least one episode of major infection every year.
- Treatment of infectious diseases has significant cost implications.

Common infections in old age are:

- lower respiratory tract infection/pneumonia
- urinary tract infection
- tuberculosis
- diarrhoea and gastroenteritis
- skin infections—herpes zoster, pyoderma, bed sore
- meningitis
- endocarditis
- septicemia
- pyrexia of unknown origin

The source of infection has a great bearing in determining the subsequent course of event.

1) **Community Acquired Infection**

Most infections are acquired in the community. The spectrum of community acquired infection can be very wide and is influenced by epidemiology of various diseases in a given geographic distribution. In general community acquired infections are due to antibiotic sensitive organisms. Community acquired infection can be sporadic or of epidemic proportion. Older subjects living in old age homes or nursing homes tend to develop infectious diseases of epidemic proportion due to close proximity and common source of infection.

2) **Hospital Acquired Infection/Nosocomial Infection**

Infection acquired during or as a result of hospitalization is termed as hospital acquired or nosocomial infection. Any infection appearing after 48 hours of hospitalization is considered as hospital acquired. The usual syndromes of nosocomial infection are pneumonia, urinary tract infection, bacteremia and wound infection. Common infectious organisms acquired in hospital are Staphylococcus aureus, E. coli, Pseudomonas, Klebsiella pneumoniae, Acinetobacter, Legionella, Candida and Aspergilus species. Hospital acquired infections are usually due to multi-drug resistant strains and are extremely difficult to treat with very high cost implications.

3.5.1 Clinical Manifestations of Infectious Disease

Many older patients present with classical manifestations of disease and pose little problem in diagnosis.

A large number of patients especially the frail ones, however, have atypical clinical and laboratory manifestations with absence of usual features of infection.

Symptoms and signs which reflect the intensity of inflammation may be mild or absent. As a result fever may not be present in serious infections and absence of fever often indicates poor prognosis. Organ specific symptoms may also be mild in intensity. Unexplained acute onset shortness of breath may be the only symptom of pneumonia and abdominal sepsis may present with fever in absence of any abdominal symptoms. Recent onset change in health and functional status may be the only manifestation of infection. Always remember to consider infection if an older patient presents with following symptoms of recent onset:

- Weakness, easy fatigability, breathlessness
- Anorexia and unexplained weight loss
- Confusion
- Avoidance of social contact and social isolation
- Incontinence
- Immobility
- Falls

Physical signs in older patients often are not diagnostic. Presence of multiple diseases causes additional problem in assigning significance to a sign. You should be always vigilant about soft signs, which may clinch the diagnosis.

The laboratory manifestation of infection may also be subtle. Leucocytosis may be absent and anaemia may be the only evidence of infection. Radiological features of tuberculosis in old age tend to be non-specific and wide spread compared to typical upper lobe fibro-cavitary lesion in younger subjects.

Higher risk of complications, slow resolution and higher risk of death is the hall mark of infectious disease in old age.

Always remember to include infection in the differential diagnosis of all ill-defined constellations of symptoms and signs in older patients.

Check Your Progress 2

1) Enumerate the organisms commonly acquired after hospitalisation.

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2) Enumerate the two most common infectious diseases in older patients.

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3.5.2 Principles of Antibiotic Therapy

Antibiotic therapy for older patient is always different from that in the younger patient, because of altered immunity, altered drug metabolism; and high risk of complications and death from infectious disease. Following are the guidelines to be considered during antibiotic prescription:

- Antibiotics should be started early for all presumed infection. After sending samples for microbiological investigations antibiotics should be started even before the investigations are available, to avoid complications and mortality from delay in treatment.

- Initial therapy should be empiric. It is always advisable to start with broad-spectrum antimicrobial agent, which covers all possible organisms responsible for that condition. The most preferred antibiotics for older patients are aminopenicillins and cephalosporins.

- Specific narrow spectrum antibiotic should be instituted only after obtaining a definitive microbiological diagnosis.

- In order to avoid inconsistency absorption of oral drug administration, injectable antibiotics should be preferred for all serious infection. However the duration of parenteral antibiotic should be short and oral antibiotic should be started early to facilitate early mobilization and avoid prolonged hospital stay.

- The chosen antibiotics should be least toxic. Potentially toxic drugs such as aminoglycosides (streptomycin, gentamycin) should be avoided. A list of antibiotics useful for elderly patients is provided in Table 3.2.

Table 3.2: Safe Antibiotics for Elderly Patients

Antibiotic Class	Name of the Drug
Penicillin and amino Penicillins	Penicillin G Ampicillin, Amoxycillin, Cloxacillin, Piperacillin, Amoxycillin + Clavulanic acid, Ampicillin + Sulbactum
Clindamycin	Cefazolin, Cephadrine Cefuroxime
Cephalosporins	Cefoperazone, Ceftriaxone, Ceftazidime
Monobactam	Aztreonam
Fluroquinolones	Norfloxacin, Ciprofloxacin, Levofloxacin
Miscellaneous	Metronidazole, Vancomycin, Erythromycin, Clarithromycin, Azithromycin, Cotrimoxazole, Trimethoprim

3.5.3 Immunization

Specific immunization against three agents have been considered important in older individuals, namely pneumococci, influenza virus and tetanus toxin.

Pneumococcal Vaccine

Pneumococcal pneumonia carries very high risk of morbidity and mortality in older patients and some other risk groups. Pneumococcal vaccine is a polyvalent vaccine containing purified capsular polysaccharide antigen from each of 23 types of pneumococci accounting for nearly 90 per cent of the isolates. Most healthy individuals in absence of immunological dysfunction mount a good antibody response which, lasts for about five years. The overall efficacy of the vaccine in preventing pneumococcal pneumonia is about 60-70 per cent but its effect is relatively poor in presence of immune dysfunction. Pneumococcal vaccine is specifically recommended in older patients with chronic renal disease including nephrotic syndrome, chronic lung disease, chronic heart disease, chronic liver disease and diabetes mellitus. Pneumococcal vaccine is administered every three years and early vaccination is contraindicated.

Influenza Vaccine

Acute respiratory tract infection due to influenza virus produces excessive morbidity and mortality in older patients with underlying cardio-respiratory disease. The composition of influenza vaccine varies from time to time depending on the global epidemic pattern. It gives a protection of 70-80 per cent against infection with susceptible strain. The vaccination though not fully protective, reduces the incidence of bronchopneumonia, hospital admissions and mortality. The protective effect of the vaccine lasts one year. Influenza vaccination is required to be administered annually. Influenza vaccine is recommended in older patients with chronic respiratory disease including bronchial asthma, chronic heart disease, chronic

renal failure, diabetes mellitus and immuno-suppression due to any cause, as the risk of influenza is much higher in presence of these conditions. Influenza immunization is also recommended for elderly living in nursing homes, residential homes and other long stay facilities as the risk of rapid spread of the disease is very high in these places. Adverse reactions are mostly encountered in individuals with egg allergy, which is the only contraindication for its use.

Tetanus Toxoid

Older subjects are liable to higher risk of accidents and injuries and may not have had vaccination in their childhood, as the vaccination programme did not exist then. Tetanus toxoid should be administered every 10 years. This provides effective protection without major side effects.

Check Your Progress 3

A 76-year old smoker with chronic bronchitis presents with history of the flu like illness for 3-4 days 2 weeks back. Subsequently he developed loss of appetite and withdrew himself from his routine activities. His family has brought him to you for abnormal behaviour and incontinence. Clinical examination revealed cyanosis, tachypnoea, confusion and features of emphysematous chest. What is your diagnosis and management strategy for next 48 hours?

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3.5.4 Approach to an Older Patient with Suspected Infection

Diagnosis is not difficult when typical symptoms and signs are present. An infectious disease should always be considered in the differential diagnosis in every older patient, whenever there are unexplained symptoms and signs. Any recent alteration in patient's functional status and mental state needs to be looked with suspicion.

In community living patients, pneumonia, urinary tract infection and tuberculosis are common. However when these conditions are excluded, abdominal infection, endocarditis and meningitis should be considered.

In hospitalized patients, urinary tract infection, aspiration pneumonia, thrombophlebitis and wound infection are the usual problems.

In nursing homes and old age homes pneumonia, urinary tract infection and pressure sores are the most likely infectious condition.

All investigation you carry out in a younger patient should also be conducted in an older patient. Age is no contraindication for arriving at a definitive diagnosis with invasive investigations for suspected infection. All attempts should be made to achieve a microbiological diagnosis through isolation and serology.

You must start the antibiotic therapy as early as possible after sending the samples for isolation without waiting for the results. At times due to logistics problem it may not be possible to carry out all microbiological investigation. In that situation, empirical antibiotic therapy must be started as a life saving measure.

Aminopenicillins (amoxycillin, ampicillin) and 2nd or 3rd generation cephalosporins (cefuroxime, cefixime, ceftriaxone, cefotaxime) are the most ideal antibiotic as broad-spectrum agent for most infection. For moderate to severely ill patients parenteral route is preferred as it prevents the possibility of inadequate drug absorption and distribution. However within, 3 to 6 days it is advisable to switch over to oral route.

It is essential that the clinical response be monitored closely to detect treatment failure and drug adverse reaction for suitable corrective action.

It is always cost effective to treat infection early in the course to avoid complication and death.

3.6 LET US SUM UP

Aging of the immune system is a complex process involving both humoral and cell mediated immunity. Along with decline in immunity, morphological changes in various organs make the elderly vulnerable to infection. In clinical practice, infections of respiratory tract and urinary tract, septicemia and tuberculosis are commonly encountered in elderly subjects. Atypical clinical presentation, slow response to treatment and high mortality is the hallmark of infection in older patients. Antibiotic therapy in elderly needs to be early, empirical and broad spectrum through parenteral route, with early change over to oral therapy. Aminopenicillins and cephalosporins are safer drugs in old age compared to aminoglycosides. Pneumococcal and influenza vaccines are recommended in elderly subjects with medical conditions with higher risk of mortality and complications.

3.7 KEY WORDS

Adaptive immunity : Recognition of the specific pathogens and reaction to eliminate it.

Cellular immunity : Immune response against organisms and tumor cells in which antibodies have sub-ordinate role.

Humoral immunity : It is mediated by B-cell and antibodies.

Immunity : Resistance of body against micro organisms is called immunity.

Septicaemia : Circulation of pathogenic bacteria causing generalized infection.

3.8 ANSWERS TO CHECK YOUR PROGRESS

Check Your Progress 1

1) Innate immunity is non-specific and is mediated by neutrophils, macrophages and NK cells. It does not require prior exposure to the infective organism neither it improves after exposure.

   Adaptive immunity is specific for the organism and requires its prior exposure. Adaptive immunity improves with each successive exposure to the organism. Key features of adaptive immunity are specificity i.e. the response is only against a particular organism

and memory i.e. the organism will be remembered forever by the immune system. B and T lymphocytes are the mediators of adaptive immunity.

2) Common drugs that cause immunodeficiency are non-steroidal anti-inflammatory drugs, steroids, antibiotics, anti-thyroid drugs, anti-depressants, anti-psychotics, diuretics, anti-convulsants, H_2-receptor blockers, oral hypoglycemic agents and calcium channel blockers.

Check Your Progress 2

1) Organisms commonly acquired in hospital are Staphylococcus aureus, E. coli, Pseudomonas, Klebsiella pneumoniae, Acinetobacter, Legionella, Candida and Aspergilus species.

2) Pneumonia and urinary tract infections are the most frequent infection in older patients.

Check Your Progress 3

The most likely diagnosis is lower respiratory tract infection subsequent to influenza, chronic obstructive airway disease, acute respiratory failure.

The patient must:

- be hospitalized
- have a chest x-ray PA view, complete hemogram (Hb, TLC, DLC, ESR), blood chemistry (blood sugar, blood urea, serum creatinine, serum sodium, serum potassium), blood culture (at least three at 6 hours interval), blood gas analysis (PO_2, PCO_2, pH)
- be started on:

  —Injectable antibiotic

  (In. Coamoxyclav 1.2 gm IV 12 hrly + Roxithromycin 150 mg P.O. 12 hrly)
  or
  (Inj. Cefuroxime 750 mg IV 12 hrly + Roxithromycin 150 mg P.O. 12 hrly)

  —Oxygen inhalation

  —Intravenous fluid $\pm$ sodium/potassium supplementation

  —Bronchodilator (salbutamol or terbulatine through nebulizer/subcuta-neous injection)
- be provided supportive management, namely, nasogastric feeding, chest physiotherapy and care of the bladder
- have close monitoring for complications
- have a repeat chest x-ray after 48 hours for reevaluation of radiological abnormalities.

3.9 FURTHER READINGS

Brocklehurst, J.C., R.C. Tallis and H.M. Fillit (eds.), *Brocklehurst's Textbook of Geriatric Medicine and Gerontology*, 5th edn., Churchill Livingstone, 1998.

Pathy, M.S.J. (ed)., *Principles and Practice of Geriatric Medicine*, 2nd ed., John Wiley & Sons, 1991.