**Lec 1 Immune disease**

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**Immunodeficiency**

The principal function of the immune system is to prevent microbial infection. Therefore, disorders resulting in impaired function of the immune system (immuno- deficiency) result in increased susceptibil- ity to infection. Immunodeficiency can arise from an intrinsic defect of a component of the immune system (primary immunode- ficiency, or PID). Alternatively, immuno- deficiency may be secondary to another pathological condition, which adversely affects immune function (Table 1). Both primary and secondary immunodeficien- cies result in increased susceptibility to infection. The precise pattern of infection depends on the specific component of the immune system that is affected. Most PIDs are caused by defects in single genes and are hence heritable. Others may represent the consequence of an interaction between the genetic phenotype and an environmen- tal influence, like viral infections. Primary immunodeficiencies are rare and based on information from national registers; these diseases are estimated to occur between 1 in 2,000 to 1 in 10,000 live births. In con- trast, secondary immunodeficiencies are more commonly seen in clinical practice. (See Table 1 for examples of secondary immunodeficiency.)

From a clinical perspective, immuno- deficiencies can be classified into eight categories (Table 2). Each category has a characteristic pattern of clinical presenta- tion (Table3), which will be elaborated on later.

**DEFECTS IN ANATOMICAL OR PHYSIOLOGICAL BARRIERS TO INFECTION**

One of the commonest predisposing causes of infection is a defect in an anatomical or physiological barrier to infection. Intact epithelial membranes, especially strati- fied squamous epithelial surfaces such as the skin, constitute an extremely effective barrier to infection. Thus, integumentary damage caused by burns, eczema, and trauma (including surgery), predisposes to infection. Skull fractures, particularly damage of the cribriform plate, may result in recurrent episodes of pyogenic menin- gitis. The existence of sinus tracts between deeper tissues and the skin surface or alternatively, the presence of foreign bod- ies or avascular areas (e.g., within bone) predisposes to infection. Obstruction to the drainage of hollow tubes and viscera also predisposes to infection, for example, obstruction of the biliary tract, urinary tract, or bronchi. Impaired vascular perfusion of the tissues due to edema and angiopathy (including microvascular changes follow- ing diabetes mellitus) also predisposes to infection. Alteration of the normal com- mensal flora by broad-spectrum antibiotic

**Table 1: Secondary Immunodeficiency**

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| --- | --- |
| **Causes of Secondary Immunodeficiency** | **Defect** |
| **Defects in anatomical and** | Various |
| **physical barriers to infection** |  |
| (see text for explanation) |  |
| **Malignancies of the B-cell** | Antibody |
| **system** |  |
| Myelomatosis |  |
| Non-Hodgkin’s lymphoma |  |
| Chronic lymphocytic leukemia |  |
| **Therapeutic agents** |  |
| **Biological agents** |  |
| Anti-B-cell antibodies: e.g., | Antibody |
| Rituximab |  |
| Anti-TNF agents | Innate immunity and CMI |
| **Cytotoxic drugs:** Alkylating | Myelosupression and CMI |
| agents, cytotoxic antibiotics, |  |
| antimetabolites, Vinca |  |
| alkaloids, etc. |  |
| **Immunosuppressive drugs:** | CMI |
| Corticosteroids, calcineurin |  |
| Inhibitors, antiproliferative |  |
| Immunosuppressants |  |
| (azathioprine, mycophenelate) |  |
| **Radiotherapy, metabolic/** | CMI |
| **nutritional deficiencies** |  |
| Renal failure | CMI and innate immunity |
| Liver failure | CMI and innate immunity |
| Protein calorie malnutrition | CMI |
| **Increased loss of** | Antibody |
| **immunoglobulin** |  |
| Protein-losing enteropathy |  |
| Nephrotic syndrome |  |
| **Virus infections** | CMI |
| HIV |  |
| CMI, cell-mediated immunity. |

therapy predisposes to colonization by antibiotic-resistant potential pathogens, which may cause infectious or toxin- induced complications, for example, pseu- domembranous colitis caused by *Clos- tridium difficile* toxin, multidrug-resistant *Staphylococcus aureus* infection. Surgical instruments, perfusion lines, and cath- eters may promote microbial invasion past the anatomical or physiological barriers Finally, damaged tissues, for example, damaged cardiac valves, provide a nidus for the establishment of infection.

Infections that recur in the same ana- tomical site are often due to defective anatomical or physiological barriers and hence should induce a diligent search for such factors. Microorganisms that cause infection in patients with this category of defects comprise pyogenic bacteria such. as staphylococci and commensal organ- isms from the skin or intestinal tract. Fungi, especially *Candida*, may be another pathogen under these circumstances

**Table.2: Operational Classification of Imunodeficiency States**

1. Immunodeficiency due to defective anatomical or physiological barriers to infection
2. Deficiency of opsonins: (a) antibody deficiency, (b) complement deficiency
3. T-cell deficiency
4. Combined T- and B-cell deficiency
5. Phagocyte deficiency
6. Defects in macrophage activation
7. Defects in immunoregulation
8. Defects in homeostasis of inflammation

**DISORDERS CHARACTERIZED BY ANTIBODY DEFICIENCY**

Antibody deficiency can be defined as a condition characterized by a reduction in serum immunoglobulin concentrations below the fifth centile for age. Antibody deficiency may affect all classes of immu- noglobulins or may be confined to a single isotype.

**Clinical Manifestations of Antibody Deficiency**

Patients with antibody deficiency typi- cally develop recurrent infection with encapsulated bacteria such as *Strep- tococcus pneumoniae* and *Haemophilus influenzae* type B. The common sites affected are the upper and lower respi- ratory tracts and the middle ear. From these sites, infection can spread via the bloodstream to produce metastatic infections, for example, meningitis or bone and joint infection.

1. Structural lung damage (bronchiecta- sis, pulmonary fibrosis) can be a con- sequence of recurrent respiratory tract infections in inadequately treated, anti- body-deficient patients, and contributes to morbidity and mortality.
2. Once respiratory tract damage is estab- lished, patients are prone to sinopul- monary sepsis caused by nontypeable *Haemophilus influenzae* strains.
3. Overgrowth of commensal bacteria in the small intestines or chronic infection by intestine pathogens (*Giardia, Salmo- nella, Campylobacter*) may give rise to diarrhea or malabsorption secondary to villous atrophy.
4. In general, the course of uncomplicated viral infection (chicken pox, measles, etc.) is not significantly different from those in normal individuals, indicat- ing that antibody production is not essential for recovery from acute viral infections. However, long-term immu- nity, which depends on the ability to develop neutralizing antibodies does not develop and the infections can recur.
5. Fungal and intracellular bacterial infec- tions are not a feature of antibody deficiency.
6. About a fifth of patients with antibody deficiency due to common variable immune deficiency (which is described in a later section) develop autoimmune disorders. These include autoimmune hematological disorders (hemolytic ane- mia, autoimmune thrombocytopenia, pernicious anemia), autoimmune endo- crinopathies (e.g., thyroid disease) or neurological diseases such as Guillain- Barré syndrome, and, rarely, a lupus- like syndrome.
7. **Table.3: Pattern of Microbial Infection in Immunodeficiency**

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| **Defect** | **Microorganism** | **Site** |
| Antibody | Encapsulated bacteria: | Upper and lower |
|  | *Streptococcus pneumoniae*, Hib, | respiratory tract |
|  | *Mycoplasma, Giardia, Salmonella,* | Less commonly |
|  | *Campylobacter* | systemic infection: |
|  |  | meningitis, bone and |
|  |  | joint infection |
|  |  | Localized or disseminated |
|  |  | Gastrointestinal tract |
| Complement | Pyogenic bacteria, especially | Septicemia, meningitis, |
| C3/Factor I | *Streptococcus pneumoniae* | pyoderma |
| C5, C6, C7, C8, | *Neisseria meningitidis* | Meningitis, septicemia |
| C2, C4 | No infections or occasionally |  |
|  | infections with *S. pneumoniae* |  |
| Properdin, factor D | Encapsulated bacterial sepsis |  |
| Phagocyte deficiency | Staphylococci, enteric bacteria, fungi | Systemic |
| Neutropenia |  |  |
| Chronic granulomatous | *Staphylococcus aureus, Salmonella*, | Skin, visceral abscesses: |
| disease | enteric bacteria, *Burkholderia* | lymph nodes, lung, liver |
|  | *cepacea*, fungi: *Aspergillus* |  |
| Leucocyte adhesin | Pyogenic bacteria | Skin; any site, localized or |
| deficiency |  | systemic |
| T-cell deficiency | Viruses, fungi, protozoa, intracellular | Any site, localized or |
|  | bacteria: *Mycobacteria, Listeria,* | systemic; mucocutaneous |
|  | *Salmonella* | candidiasis |
| Defects in macrophage | Intracellular bacteria: *Mycobacteria,* | Lymph node; bone; |
| activation: Type I | *Listeria, Salmonella* | disseminated |
| cytokine deficiency |  |  |
| Combined T- and B- | As for antibody and T-cell deficiency | As for antibody and T-cell |
| cell deficiency |  | deficiency |
| Hib, *Haemophilus influenzae type B* |