Immunodeficiency

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Origins of Immunodeficiency

• Primary or Congenital
  – Inherited genetic defects in immune cell development or function, or inherited deficiency in a particular immune molecule

• Secondary or acquired
  – A loss of previously functional immunity due to infection, toxicity, radiation, splenectomy, aging, malnutrition, etc.

Infectious Consequences of Immunodeficiency

• Antibody deficiency, Phagocyte deficiencies, or Complement protein deficiencies are associated with recurrent infections with extracellular pyogenic bacteria (pneumonia, otitis media, skin infections)

• Deficiency in Cell-mediated immunity is associated with recurrent or chronic viral, fungal, or protozoal diseases.

<table>
<thead>
<tr>
<th>Name of deficiency syndrome</th>
<th>Specific abnormality</th>
<th>Immune defect</th>
<th>Susceptibility</th>
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</thead>
<tbody>
<tr>
<td>Severe combined immune deficiency</td>
<td>ADA deficiency</td>
<td>No T or B cells</td>
<td>General</td>
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<td></td>
<td>Fatty acid deficiency</td>
<td>No T cells</td>
<td>General</td>
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<td></td>
<td>T-cell receptor deficiency</td>
<td>No T cells</td>
<td>General</td>
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<td></td>
<td>Autoimmune deficiency</td>
<td>No T or B cells</td>
<td>General</td>
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<tr>
<td>Digeorge's syndrome</td>
<td>Thymic aplasia</td>
<td>Variable numbers of T and B cells</td>
<td>General</td>
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<td>MHC class I deficiency</td>
<td>TAP mutations</td>
<td>No CD8 T cells</td>
<td>Chronic lung and skin inflammation</td>
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<tr>
<td>MHC class II deficiency</td>
<td>Lack of expression of MHC class II</td>
<td>No CD4 T cells</td>
<td>General</td>
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</tbody>
</table>
B cell Deficiencies

- **Congenital hypogammaglobulinemia**
  - Symptoms at 9 mo. to 2 yr of age
  - Treat with intravenous immunoglobulin (IVIG)
- **Hyper IgM**: defective CD-40L expression
- **Selective IgA deficiency**
  - Occurs in 1:600-1:800 people
  - Possible connection with increased sinopulmonary infections and allergies
T Cell Deficiencies
- Congenital Thymic aplasia
- Chronic Mucocutaneous Candidiasis

Severe Combined Immunodeficiency
- X-linked SCID:
  - Defect in IL-2 receptor
- Swiss-Type SCID
  - Adenosine deaminase deficiency
- Bare Lymphocyte syndrome
  - Absence of MHC Class II gene products

Phagocyte Deficiencies
- Chronic Granulomatous Disease
  - NADPH oxidase defect
- Chediak -Higashi Syndrome
  - Abnormal lysosome formation
- Leukocyte Adhesion Deficiency
  - Absence of leukocyte adhesion molecules

Complement Deficiencies
- Single component deficiencies
  - Example: C3 deficiency
- Hereditary Angioedema
  - C1 Inhibitor deficiency
- C5,C6,C7,C8, or C9 deficiency
  - Recurrent bacterial meningitis due defective membrane attack complex
Causes of Acquired Immunodeficiency

- Cancer (immunoproliferative diseases)
- Cytotoxic drugs or radiation
- Malnutrition
- Splenectomy
- Immunosuppressive therapies
- Stress/emotions
- Aging (thymic atrophy)
- Infection

Immunopathogenesis of HIV-Infection

- HIV infects and ultimately destroys CD4+, CCR5+ or CXCR4+ T cells, monocytes, & dendritic cells.
- Primary HIV Infection: A vigorous immune response to HIV controls the primary infection. (clonal Cytotoxic T cells, suppressive chemokines, poorly neutralizing antibody)

Immunopathogenesis of HIV-Infection. (continued)

- Chronic Asymptomatic Phase: Viral trapping & replication in lymphoid tissues, high rate turnover of virus and CD4 T cells, loss of CD4 functional help to CTL and antibody responses, destruction of lymph tissue, viral mutation and escape from recognition, exhaustion or viral inhibition of CD4 T cell renewal.

Immunopathogenesis of HIV-Infection. (continued)

- Overt AIDS: CD4 count declines, viral load increases, opportunistic infections.
Dendritic Cells transport HIV from Mucosal to Lymphoid Tissues

HIV binds CD4 and co-receptor (chemokine receptor) to enter host cells
Mechanisms of CD4+ T cell depletion - Dysfunction

- Accumulation of unintegrated viral DNA
- Loss of plasma membrane integrity due to viral budding
- Elimination of infected cells by HIV-specific immune effectors
- Syncytium formation
- Autoimmunity

Mechanisms of CD4+ T cell depletion - Dysfunction (continued)

- Superantigenic stimulation
- Apoptosis
- Infection of stem cells and interference with lymphopoiesis
## Opportunistic Infections in AIDS Patients

<table>
<thead>
<tr>
<th>Infections</th>
<th>Malignancies</th>
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</thead>
<tbody>
<tr>
<td><strong>Pneumonia</strong></td>
<td>Kaposi's sarcoma, HHV6, Non-Hodgkin's lymphoma, including EBV-positive Burkitt's lymphoma, Primary lymphoma of the brain</td>
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<tr>
<td><strong>Protozoa</strong></td>
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<tr>
<td>Toxoplasma spp.</td>
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<td>Cryptosporidium spp.</td>
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<td>Leishmania spp.</td>
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<td>Microsporidium spp.</td>
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<tr>
<td><strong>Viruses</strong></td>
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<td>Herpes simplex</td>
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<td>Cytomegalovirus</td>
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<td>Varicella zoster</td>
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<tr>
<td><strong>Fungi</strong></td>
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<tr>
<td>Pneumocystis carinii</td>
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<tr>
<td>Cryptococcus neoformans</td>
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<tr>
<td>Coccidioides capsulata</td>
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<tr>
<td>Histoplasma capsulatum</td>
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<tr>
<td>Coccioides immitis</td>
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