Clinical immunology
Outline

• Terms and definitions
• Evolution
• Overview of investigations
• Disorders of immune system
  – Immune deficiencies
  – Autoimmunity
  – (Allergy)
  – (Malignancy)
  – (Transplantation medicine)
Terms and definitions

- Complex system of cells and molecules with special roles in defense against infection
- Levels of defence
  - Skin and mucosal surfaces (enzymes, pH, mucus, cilia) – antimicrobial properties, inhibition of microbial adhesion
  - Non-specific (innate) immunity – same type and extent of action in repeated microbe exposure
  - Specific (adaptive, acquired) immunity – improves efficacy in repeated microbe exposure
Mechanisms of innate immunity

- **Phagocytic system**
  - Neutrophil leucocytes
  - Monocytes
  - Macrophages

- **Mediator-releasing cells**
  - Basophilic granulocytes
  - Mast cells
  - Eosinophilic granulocytes

- **Complement, acute-phase proteins, cytokines (interferons)**
Acquired immunity

• Proliferation of Ag-specific B and T cells
  – Response to Ag presentation by APC
  – B-cells – Ig production (extracellular pathogen elimination)
  – T-cells:
    • Provide help to Ab production
    • Destroy intracellular pathogens (Macrophage activation, destruction of virus-infected cells)
Immune system evolution

- Source: Pluripotent stem cell of yolk sac (week 3) to fetal liver (week 5)
- Sites of maturation in primary lymphoid tissue (week 8-11):
  - B-cells: bone marrow
  - T-cells: thymus
- Sites of acquired immune response: secondary lymphatic organs:
  - LN, spleen, MALT
T-cell development

• Thymus seeded by blood-borne T-cell precursors from fetal liver (pro-T cells), evolution of TCRs (through TCRgene rearrangement-random combinations → enormous TCR diversity)

• Upon TCR expression – selection processes start
  – **Positive selection** – interaction of immature thymocytes expressing low levels of TCR with MHC on thymic epithelium (CD4 – HLA II, CD8 – HLA I) – selection of **cells capable to interact with foreign antigens** presented on self MHC
  – **Negative selection** – thymocytes with high TCR expression reacting with self peptides presented by HLA I or II of thymic macrophages induces apoptosis – deletion of **autoreactive cells**

• Migration of T cells to secondary lymphoid organs
B-cell development

- Fetal liver stem cells (wk 7) seed bone marrow

- **Antigen-independent** development
  (immunoglobulin gene rearrangement processes) reached by wk 14 – mature (virgin) B cell

- **Antigen-dependent** development – after stimulation by Ag through antigen receptor (sIg)
  - Differentiation into memory cells (for particular Ag) and plasma cells (secreting Ag-specific Ig=antibody)
  - Ig isotypes: M,G,A,D,E
Immunoglobulins

• IgG+M = the only C-fixing Igs, main protection against infection
• IgM-intravascular, IgG – all fluids
• IgA – surface protection (secretions)
• IgE – defense against parasites, mediator of immediate type of allergic reaction
• Maternal IgG cross placenta from wk 12 by birth when reach maternal level
Immune cell interactions

- BCR (sIg) – recognizes native Ag
- TCR – recognizes only processed antigenic peptides presented by MHC molecules
  - Class I: HLA –A, -B, -C antigens
  - Class II: HLA –DR, -DP, -DQ antigens
- Presentation by antigen-presenting cells (APCs)
Ag presentation

• MHC molecules – groove to fit with peptide
• HLA I: expressed by most nucleated cells
  – Degraded cell peptides incl. Viral peptides in infected cells
• HLA II: macrophages, dendritic cells, B-cells
  – Peptides from exogeneous native antigens (bacterial proteins)
Ag presentation
• **Primary Ab response:** native Ag is carried to the draining LN, taken up by specialised cells (FDCs), expressed and presented to virgin B-cells→evolution into plasma cell, production of Ag-specific IgM (low-affinity)

• Some B-cells become memory cells
  – Can switch Ig genes to IgG, A or E production

• **Secondary Ab response** – upon memory B-cell encounters Ab again
  – More cells generated, somatic mutation of Ig genes increases affinity
Postnatal lymphopoiesis

- **T-cell (CD3+)** number in cord blood higher in infants
  - CD4:CD8 higher
  - Ability of cord blood T-cells to respond to mitogens and to develop Ag-specific response (BCG)
Postnatal lymphopoiesis

- **B-cells**
  - Higher in cord blood, do not make full Ig range, start with IgM in response to Ag stimulation from environment (premature have this ability)
  - Total Ig level at minimum around 3-4 mo
  - Ability to produce Ab against protein Ag – from birth, against polysaccharides from 2y (conjugated vaccines e.g. HIB)
  - Newborns susceptible to G- organisms because lack of IgM (=opsonins)-impaired phagocytosis by PMN
  - Mother IgG serve as opsonins for most G+ bacteria, specific IgGs against common viral infections suffice
  - Premature infants receive less IgG-lower opsonic activity to all types of organisms
Evolution of antibody production

- Fetal Ab = IgG transplacental
Lymphoid organ development

- **Thymus** – at birth 2/3 of mature weight, peak mass just before puberty, then gradual involution
- **Peripheral lymphoid tissue** – adult size reached by 6 yrs, exceeds those dimensions during prepubertal years, involution coincident with puberty
- **Spleen** gradually grows until adulthood
- **Peyer patches** gradually grow, largest during adolescence
Immunopathology

Homeostasis dysregulation

• Immune deficiencies
• Alergies
• Autoimmunity
• Neoplasia
• Graft rejection
Immunodeficiencies
Evaluation of suspected immunodeficiency

• Major cause of recurrent infections: excessive exposure to infectious agents in group settings

• Indications for immunologic evaluation
  – ≥2 systemic or serious bacterial infections
  – ≥3 serious respiratory or bacterial soft tissue infections in 1 year
  – Infections at unusual sites (liver, brain abscess)
  – Infections with unusual pathogens
  – Unusually severe infections with common pathogens
Screening evaluation

- Thorough history
- Physical exam
- Laboratory screening
  - FBC, diff, ESR
  - B-cells: IgA (G,M), isohemagglutinin, Ab to tetanus, diphteria, H.Infl., S.pneumoniae
  - T-cells: Abs L count, Candida intradermal skin rest (or MxII)
  - Phagocytes: Abs N count, respiratory burst assay
  - Complement: CH$_{50}$
FBC, ESR

• Normal L count: T-cell defects unlikely
• Normal N count: precludes neutropenia, leucocyte adhesion deficiency
• Normal Plt count: excludes Wiscott-Aldrich syndrome
• Normal ESR: chronic bacterial or fungal infection unlikely
Primary defects of antibody production

- Most frequent of the primary ID
- **Clinically:** recurrent infections with encapsulated bacteria or history of failure to respond to ATB
- Selective IgA deficiency – most common (1/300-1/16000), agammaglobulinemia (1/50000)
- **Genetic defects** recognised for many, not only in B, but also T-cells providing help
- **Therapy:**
  - antibiotics + regular Ig replacement therapy (IVIG)
  - Bone marrow transplantation for CD40 ligand defect and XLP
XLA (Bruton)

- Profound defect in Bcell development, absence of circulating B cells, small to absent tonsils and no palpable LN
- Defective gene (long arm X chr) for tyrosin kinase (Btk), necessary for maturation
- Most affected boys well over initial 6 mo of life, then infections with extracellular pyogenic organisms
- Dg: screening, FACS, prenatal mutation analysis in male fetuses of carrier mothers (chorionic villus)
CVID

- Hypogammaglobulinaemia with phenotypically normal B cells
- Later age at onset of infections
- Equal sex distribution, less severe infections than in XLA
- In most cases no identified molecular defect
- Connection to isolated IgA deficiency
- Serum Ig low, autoAb formation possible, normal or enlarged tonsils and LN, splenomegaly, higher rate of lymphomas
• **Selective IgA deficiency**
  – Genetic basis unknown
  – Respiratory, GI, urogenital infections
  – High incidence of autoimmune diseases, increased malignancies
  – Ab against IgA in 44% (blood products highly purified)

• **Transient hypogammaglobulinaemia of infancy**
  – Extension of physiologic hypogammaglobulinaemia

• **IgG subclass deficiencies**

• **Hyper IgM syndrome**
  – Genetically heterogenous
  – X-linked – T-cell defect of CD40L (inability of T-cells to provide help necessary for switch of Ig isotype), recurrent pyogenic infections from 1 year, small LN and tonsils, normal number of B-cells, often neutropenia, susceptibility to P.carinii
  – X-linked from mutations in gene for NF-κB essential modulator (NEMO deficiency)
  – AR from mutations in the gene for AID, CD40
Primary defects of cellular immunity

- Generally more severe infections, often fungi, viruses, pneumocystis
- **Thymic hypoplasia (DiGeorge syndrome)**
  - Dysmorphogenesis of the 3rd and 4th pharyngeal pouches in early embryogenesis
  - Parathyroid glands and often other structures (aortic arch, heart, oesophagus, uvula..) also affected
  - Often hypocalcemic seizures in neonate
  - Variable degree of thymic deficiency („partial“ syndrome)
  - Therapy: HLA-identical sibling BMT, thymic tissue transplants
- Defective cytokine production, T-cell activation defects
Primary combined immunodeficiencies

- Severe, often opportunistic infections, death in early infancy or childhood unless early BMT provided

**SCID**
- Diverse mutations, absence of all adaptive immune functions (X-linked-common cytokine receptor gamma chain 45%, AR – ADA deficiency 15%...)
- In some – lack of NK cells
- Small thymus, underdeveloped lymphoid tissues
- Early presentation with various severe infections with wasting, persistent opportunistic infections (cave BCG), GVHD from maternal T cells or non-irradiated blood products
- Lymphopenia at birth
- Therapy: pediatric emergency, without BMT death before 1st year
- Gene therapy in the future
Acute inflammatory response
Phagocyte function disorders

• **Leukocyte adhesion deficiency**
  - LAD1 (integrin CD18), LAD2, AR disorders, 1/10 million, recurrent bacterial and fungal infections, depressed inflammatory response with marked neutrophilia

• **Chédiak-Higashi syndrome**
  - AR disorder, defective degranulation of neutrophils, mild bleeding diathesis, oculocuataneous albinism, peripheral neuropathy, lymphoma-like syndrome

• **Chronic granulomatous disease**
  - Inability of Ne and Mo to kill ingested microbes, accumulation of ingested material, formation of granulomas
  - Defet of the generation of oxygen metabolites
  - Incidence 4-5/1 million, X-linked in 2/3, 1/3 AR
  - Recurrent/unusual lymphadenitis, multiple osteomyelitis, hepatic abscesses, unusual Staph infections
  - Onset from early infancy to adulthood
  - NBT test, DHR test (flow cytometry)
  - Therapy: supportive care + IFN gamma followed by BMT,
Leucopenia

• Note developmental changes

**Neutropenia**: acute, chronic, drug-induced
  – Infections primarily from endogeneous flora and nosocomials. Fever, soft tissue, mucous memb and skin, respiratory and GI tract, most comonly Staph, G- bact
  – Therapy: rhG-CSF, ATB

• **Immune-mediated**
  – Circulating antineutrophil Ab
  – ANN (alloimmune neonatal) – transfer ofmaternal Ab, isolated, ANI (infancy)

• **Ineffective myelopoiesis** (vit B12, folic acid def., malabsorption...)

• **Intrinsic disorders of myeloid stem cells**
  • Cyclic neutropenia- AR, regulatory abnormality
  • Severe congenital neutropenia – Kostmann disease
  • Schwachman-Diamond diseese – AR, GI disorder + neutropenia, by 4 mo, chondrodysplasia
  • GSD Ib(vonGierke)
Lymphopenia

- 65% of CD3 (T cells) are CD4 helper T lymphocytes
- Often no specific symptoms
- Inherited causes
- Acquired: AIDS (destruction of infected CD4), other infections, therapy side effects, immune-mediated
Complement disorders

• Primary deficiencies – of all 11 components of classical membrane attack pathway possible
  – C1q (and other components) deficiency – SLE-like syndrome
  – Recurrent Neisseria infections typical

• Deficiencies of C control proteins
  – Properdin def – predisposition to meningococcal infection
  – Hereditary angioedema – abnormal synthesis of C1 inhibitor (5-30%), acquired form possible