**Neutrophil Function Disorders**

**Introduction:** Rare condition

**Risk Factors:** Congenital and/or hereditary

**Biology:**
- Functional maturation:
  - Phagocytosis → Chemotaxis → O2 independent killing → Acquisition of Respiratory Burst (Start from promyelocyte).
  - Primary granule mRNA → 2nd granule mRNA.

**Clinical Presentation:** Recurrent infection. See individual diseases.

**Diagnosis:**
- Family history
- Specialised neutrophil function rest, respiratory burst assay, etc.
- Bone marrow biopsy

**Pathology:** Specific testing required.

**Prognosis:** N/A

**Tx Principle:**
1). Leukocyte Adhesion Deficiency (LAD): neutrophil unable to leave vasculature to migrate into tissue → neutrophilia
   - LAD I: mutation in ITGB2 (common β2 integrin subunit) → defective CD18 → No/low CD11/CD18
     * Sx: AR. Recurrent bacterial infection, ANC >30,000 without tissue PMN (no pus), impaired wound healing.
   - LAD II: defective fucosylation of selectin receptor
     * Sx: frequent infection (less severe) plus short stature, mental retardation.
   - LAD III: defective integrin activation → affect both leukocyte and platelet.
     * Sx: AR. Severe infection + defective platelet function (bleeding diathesis).
     * Dx: Flow cytometry: intact integrin expression but impaired activation. Kindlin-3 mutation testing.
   - Tx: Antibiotics. HCT (treatment of choice). G-CSF (experimental)

2). Chronic Granulomatous Disease (CGD):
   - Path: defect in phagocyte NADPH oxidase → absent or defective respiratory burst
   - Genetics: X-linked. Female carrier do not have ↑ rate of infection.
   - Sx: recurrent life-threatening infection with catalase + organisms, fungal infections, granuloma formation
     * Usual sites of infection: lung, skin, lymph nodes, and liver (staphy liver abscess)
3). Chediak-Higashi Syndrome (CHS):
   - Path: Defective gene (CHS1/LYST) → impaired vesicle trafficking → impaired granule secretion → giant cytoplasmic inclusion granules in neutrophils (pathognomonic).
   - Sx: AR. Recurrent infections, partial albinism, progressive neurologic abnormalities, mild coagulation defects, and a lymphoma-like accelerated phase.
   - Accekerated phase: massive nonclonal lymphohistiocytic infiltration of virtually all organs → multiorgan failure (hepatosplenomegaly, pancytopenia, bleeding diathesis, hemophagocytic lymphohistiocytosis).
   - Dx: PBS → giant cytoplasmic inclusion granules in neutrophils (pathognomonic)
     Confirmation → Gene sequencing of CHS1/LYST
   - Tx: supportive, allo-SCT

4). Hyperimmunoglobulin E Syndrome (Job Syndrome)
   - Path: STAT3 & DOCK8 mutation → Defective neutrophil chemotaxis
   - Sx: Recurrent skin and pulmonary infections (bacterial), eczematous dermatitic, and elevated IgE, coarse facial features, recurrent fractures, hyperextensible joints.
   - Dx: ? Gene sequencing
   - Tx: ?

5). Myeloperoxidase deficiency (MPO): AR
   - Patho: MPO deficiency → Primary granule enzyme defect
   - Sx: Asymptomatic (95%). ↑ mucocutaneous infection with candida can in ps with concurrent DM
   - Tx: none

6). Neutrophil-Specific Granule Deficiency:
   - Path: Mutation of C/EBP-є (loss of function) → Abnormal neutrophil without secondary and tertiary granules (but normal azurophilic granules).
   - Sx: severe skin and lung infection (staphy)

7). Auto-inflammatory Diseases (Periodic fever syndrome): recurrent unprovoked inflammation without infection
7.1 Familial Mediterranean Fever (FMF): AR
   - Path: MEFV gene mutation → altered pyrin (cyto-skeletal protein) → activation of IL-1β (via NF-κB) → PMN-mediated inflammation (unpredictable neutrophil activation and tissue infiltration).
   - Sx: Paroxysmal fever; Neutrophilia; Serositis (acute peritonitis, ankle synovitis)
     * ↑ Risk for renal AA amyloidosis.
   - Clinical criteria: Major (1) Fever w/sorositis; (2) AA amyloidosis; (3) + colchicine
response; Minor (a) recurrent fever; (b) erysipelas; (c) +FH
  - Dx: 2 major or 1 major + 2 minor criteria
  - Confirmation: MEFV mutation testing
  - Tx: Colchicine → prevents clinical attacks and tissue amyloid deposition. HCT for refractory dz.

7.2 Hyper-IgD Syndrome: AR
  - Path: Mutation in mevalonate kinase (MVK) gene → Autoinflammatory in Dutch and French

7.3 TNF-receptor-associated periodic syndrome (TRAPS, familial Hibernian fever): AD
  - TNF receptor mutation → Autoinflammatory in Scottish and Irish

8). WHIM Syndrome:
  - Path: Mutation in CXCR4 (receptos for SDF1 regulating release of neutrophil from bone marrow) → ↓ release of neutrophil from bone marrow → neutropenia, and abnormal retention of neutrophil in BM. Also lymphopenia and T-cell dysfunction.
  - Sx: Recurrent bacterial infections, Warts (extensive), Hypogammaglobulinemia, and Myelokathexis.
  - Dx: clinical + CXCR4 mutation testing
  - Tx: G-CSF for neutropenia.

**Follow-Up:** N/A