Neutropenia

Introduction: Neutropenia is an abnormally low number of circulating neutrophils less than 1500. Fever in a patient who is neutropenic due to chemotherapy, hematopoietic cell transplant, or bone marrow suppression from any cause is a medical emergency.

Risk Factors: A. Neutropenia - Diff Dx
   A) Secondary neutropenia:
      - Infection-induced: EBV, HIV, H.Pylori, CMV, parvovirus, etc.
      - Drug-induced: cocaine with levamisole → agranulocytosis).
      - Nutritional deficiency: B12, folate, copper deficiencis
      - Pregnancy-induced
      - Hyersplenism
      - Immune-mediatied:
        * Primary neutropenia (√ Ab against neutrophil - NEVER done)
        * SLE, RA, etc.
        * T-LGL (cytotoxic T cells)
        * Neonatal Alloimmune Neutropenia (from mother IgG)

   B) Congenital Neutropenia:
      - Severe congenital neutropenia
      - Cyclic neutropenia
      - Myeloperixidase deficiency → severe neutropenia

   C) Benign neutropenia: familial, ethnic (africa american)

   D) Primary neutropenia
      1) Constitutional: associated with
         - Down syndrome, Transient MPD, Sweet's syndrome (fever, neutrophilia, painful skin plaques)
      3) Primary neutrophil disorders:
         - FMF (auto-activation/auto-inflammation)
         - LAD (can't emigrate into tissue)
         - CGD (can't kill)
         - Pelger-Heut anomaly: mutation in lamin B-receptor gene → a benign dominantly inherited defect of terminal neutrophil differentiation → bilobed nucleus → function normally.
         * Pseudo-Pelger cells: seen in acute infection, myeloid leukemia, myelofibrosis, MDS

Biology: A) Myelopoiesis:
   1) HSC → Myeloblast → Promyelocyte → Myelocyte → Metamyelocyte → Band →
Segmented Neutrophil (PMN).
2) Functional maturation: Phagocytosis → Chemotaxis → O2 independent killing → Acquisition of Respiratory Burst (Start from promyelocyte).
3) Primary granule mRNA → 2nd granule mRNA.

B) Left shift (↑ band → bandemia), leukemoid reaction (↑ up to promyelocyte), acute leukemia

C) Neutrophil Life Span:
- Myeloid precursors: 20%, maturation in BM, 7-10 days
- Storage pool: 75%
- Marginating pool: 3%
- Circulation pool: 2%, 3-6 hrs
- Duration in the tissue: 2-3 days

Clinical Presentation:
- Recurrent infection
- Neutropenia fever

Diagnosis:
A. Neutropenia: <1500
1) Definitions:
- 1000-1500: → no significant infection
- 500-1000: → some ↑ risk of infection → fever mgt as outpt
- < 500 (acute): → significant ↑ risk of infection → fever mgt as inpt → IV Abx
  * if chronic <500, most pts do well until ANC < 200
2) Work-up: for stable neutropenia → √ H&P, CBC, ESR q 2-12 wks
- further eval → collagen vascular, nutritional deficiency, , US spleen, HIV, bone marrow biopsy

B. Leukocytosis Evaluation:
- Repeat CBC, √ ESR, CRP
- Eval for acute/chronic infection or inflammation
- LAP score: of limited
- FISH for bcr-abl (important)
- Bone marrow biopsy:

Pathology: Tumor (LAP ↑/normal), Leukemoid reaction

Prognosis: Various.

Tx Principle: A. Primary Neutropenia:
1) Severe Congenital Neutropenia (SCN): include Kostman syndrome
1.2. Clinical:
- Severe neutropenia at birth (ANC <200) → severe infection (G-CSF →↑ survival).
  - ↑ risk of AML/MDS, a/w acquired G-CSF R mutation, monosomy 7, or G-CSF refractory (ANC <2188 x 6 months despite tx). Note: G-CSF itself does not cause leukemic transformation.
1.2. Classification:
- SCN (AD): mutation in neutrophil elastase gene (ELA2) → neutrophil apoptosis. AML is a/w truncated G-CSF receptor.
- Kostman syndrom (AR): mutation in HAX1 (a mitochondrial protein) → destabilize mitochondrial membrane → severe neutropenia + neurological sx.
1.3 Dx: ** Gene mutation testing (ELA2) !
- BM: Myeloid maturation arrest at promyelocyte or myelocyte stage.
1.4 Tx: * G-CSF (require yearly BM biopsy surveillance during G-CSF tx), * Allo-SCT from HLA-identical sibling, unrelated donor is NOT recommended.

2). Cyclic Neutropenia (CN):
2.1 Clinical: * Cyclic neutropenia q 21 days (ANC < 200-500, reciprocal cyclic monocytosis), * Benign course, no ↑ risk of AML, * Can evolve into chronic persistent neutropenia.
2.2 Path: ELA2 gene mutation (different that in SCN) → periodic myelocyte arrest.
2.3 Dx: * Serial blood counts, * ELA2 gene mutation testing (confirmation).
2.4 Tx: G-CSF (low dose) for severe infection

3). Immune-mediated Neutropenia (AIN): * Primary (children), * Secondary (adult)
3.1 Primary Autoimmune Neutropenia:
- Path: anti-neutrophil antibodies against FCyRIII → ↑ neutrophil clearance. BM: normal.
  - Sx: ANC 500-1000 in children (6-12 months).
  - Dx: clinical dx. NEVER check anti-neutrophil antibody.
  - Tx: spontaneous remission in 2 yrs (95%). G-CSF for recurrent infection.

3.2 Neonatal Alloimmune Neutropenia:
- Path: from mother IgG against. BM: late myeloid arrest.
- Sx: omphalitis, skin infection, or life-threatening infection
- Tx: Spontaneous recovery in 3-28 weeks. Abx, G-CSF for recurrent infections.

3.3 Autoimmune Neutropenia in SLE (Secondary)
- Marker for disease activity but NO impact on disease course
- Infectious complication of SLE correlates with immunosuppression therapy, NOT neutropenia
  - Anti-neutrophil antibody may present, but poorly c/w neutropenia, poor specificity.

3.4 Autoimmune Neutropenia in RA (Secondary)
- Felty syndrome: neutropenia, RA (severe), splenomegaly, plus polyclonal LGL
  * High mortality from infection.
- LGL-associated neutropenia: older pts (>60yrs), indolent (mOS >10yrs)
  * RA, splenomegaly, neutropenia, plus monoclonal TGL (leukemia)
- Diff Dx: * LGL: monoclonal disorder - T cell (CD3+CD57+) or NK cell (CD3-CD56+);
  * ↑ clonal cytotoxic T lymphocyte → ↑ neutrophil destruction.
  - Tx: Observe for asymptomatic pts. For symptomatic cytopenia, → MTX +/-
4) Drug-induced Neutropenia: → profound neutropenia or agranulocytosis
   - Occurs within 3-6 months after starting the offending drug, and resolves in 1-2 wks after withdraw the drugs.
   - Common drugs causing agranulocytosis: * Anti-thyroid meds (carbamizole, methimazole, thiouacil); * Antibiotics (cephalosporins, penicillins, sulfonamides, chloramphenicol); * Anti-convulsants (carbamazapine, valproic acid); * cocaine
   - Tx: stop the offending drugs.

5) Chronic Idiopathic Neutropenia: ANC <500 without other primary or secondary causes
   - Sx: Benign
   - Tx: No tx. G-CSF reserved for recurrent infection pts

B) Neutropenia fever
   - Will be discussed in the section of hematology emergency.

Follow-Up: Monitor CBC.