Overview & Rationale

Although it is inaccurate to use the terms “leukopenia” and “neutropenia” interchangeably, both deficiencies usually come alongside in the clinical realm: The vast majority of patients with leukopenia also have neutropenia because neutrophils are far more numerous in the blood than lymphocytes, and neutrophils also comprise the bulk of granulocytes.

Even though variations of leukopenia can arise, e.g. lymphopenia without neutropenia, these are more rare and the differential is generally less broad than it would be for leukopenias involving neutropenia.

For these reasons, the main focus of this one-pager is neutropenia.

Definitions

1) **Leukopenia**: low total white blood cell (WBC) count in the peripheral blood, generally <4.0 x 10⁹/L

2) **Granulocytes**: neutrophils, basophils and eosinophils, also referred to as polymorphonuclear cells (PMNs)

3) **Absolute Neutrophil Count (ANC)**: = WBC x percentage of (PMNs+bands)

4) **Neutropenia**: disease graded according to ANC:
   - mild: 1.0-1.5 x 10⁹/L
   - moderate: 0.5-1.0 x 10⁹/L
   - severe: < 0.5 x 10⁹/L
   - very severe: < 0.2 x 10⁹/L

Infection risk usually increases with neutropenia in the moderate range or below, however, this is also dependent upon bone marrow granulocyte reserve.

Disease Classifications & Diagnostic Considerations

1) **Neutropenia- Acquired**

<table>
<thead>
<tr>
<th>CLASSIFICATIONS</th>
<th>ADDITIONAL INFO</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Immune-associated (i.e. alloimmune and autoimmune)</td>
<td></td>
</tr>
<tr>
<td>i) Alloimmune, i.e. neonatal</td>
<td></td>
</tr>
<tr>
<td>ii) Primary autoimmune neutropenia/chronic benign neutropenia of infancy &amp; childhood</td>
<td></td>
</tr>
<tr>
<td>iii) Secondary autoimmune neutropenia</td>
<td></td>
</tr>
<tr>
<td>iv) Other autoimmune</td>
<td></td>
</tr>
<tr>
<td>b) Chronic idiopathic neutropenia</td>
<td></td>
</tr>
<tr>
<td>c) Drug-induced (Immune-mediated vs. bone marrow suppression)</td>
<td></td>
</tr>
<tr>
<td>d) Chemotherapy-induced</td>
<td></td>
</tr>
<tr>
<td>e) Iatrogenically-induced (non-drug, non-chemotherapy)</td>
<td></td>
</tr>
<tr>
<td>f) Toxin-induced</td>
<td></td>
</tr>
<tr>
<td>g) (Post-)Infection</td>
<td></td>
</tr>
<tr>
<td>h) Nutritional deficiencies</td>
<td></td>
</tr>
<tr>
<td>i) Primary bone marrow and hematological disorders &amp; malignancies</td>
<td></td>
</tr>
</tbody>
</table>

   - Recurrent infections dissipate spontaneously w/ age
   - Pure white cell aplasia
   - T-gamma lymphocytosis
   - Bone marrow infiltration by lymphocytes; can be associated w/ RA
   - No spontaneous remission
   - Significant infections unusual, perhaps due to N bone marrow granulocyte reserve
   - Anti-microbials, e.g.: penicillins, acyclovir, metronidazole
   - Analgesics/anti-inflammatories, e.g.: ASA, ibuprofen, indomethacin
   - Antihistamines, e.g.: ranitidine, cimetidine
   - Psychotropic meds, e.g. clozapine, haloperidol, risperidone
   - Anti-HTN/cardiac meds, e.g. propanolol, thiazides, spirinolactone
   - Anti-convulsants, e.g. carbamazepine, phentoyin, valproic acid
   - E.g. febrile neutropenia (most common in chemo pts but can also occur in pts w/ hematological malignancies, or in pure white cell aplasia)
   - Various definitions, but generally accepted: single oral T ≥38.3°C or T ≥38°C sustained over 1 h & ANC <0.5 x 10⁹/L or ANC <1 x 10⁹/L & expected to drop to ≤ 0.5 x 10⁹/L
   - E.g. hemodialysis, filtration leukapheresis, transfusion reaction
   - Mercury, arsenic and ETOH
   - May be due to transiently increased utilization &/or hypersplenism
   - Viral- e.g. HIV, measles, EBV, hep, RSV, parvovirus, influenza
   - Bacterial- e.g. shigella, brucellosis, TB
   - Parasitic- e.g. malaria
   - Rickettsial
   - E.g. B12, folate, copper, protein
   - E.g. aplastic anemia, myelodysplasia/MDS, leukemia (late-stage), multiple myeloma

Dr. Michael Evans developed the One-Pager concept to provide clinicians with useful clinical information on primary care topics.
II) Neutropenia- Congenital

<table>
<thead>
<tr>
<th>CLASSIFICATIONS</th>
<th>ADDITIONAL INFO</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Cyclic neutropenia (CN)²</td>
<td>Recurrent oral infections &amp;/or cellulitis &amp;/or vaginitis + fluctuations in numbers of various types of blood cells approx q21d³</td>
</tr>
<tr>
<td>b) Severe congenital neutropenia (SCN)² (Kostmann’s syndrome¹)</td>
<td>High infection risk¹⁰</td>
</tr>
<tr>
<td>c) Shwachman-Diamond syndrome (SDS)¹</td>
<td>Triad of neutropenia, metaphyseal dysplasia &amp; pancreatic insufficiency¹⁰, Dx: bone marrow aspirate usually = myeloid hypoplasia¹¹</td>
</tr>
<tr>
<td>d) As part of other congenital syndromes⁵</td>
<td>Various syndromes, e.g. Cohen = Hypotonia, microcephaly, mental retardation¹⁰, Dx: bone marrow aspirate usually = myeloid hypoplasia¹¹</td>
</tr>
</tbody>
</table>

III) Physiologic Neutropenia

Many people of African descent tend to have mildly low neutrophil counts¹² (often 1.0-1.5 x 10⁹/L) with no increased infection risk². Some populations of Arab & Yemenite Jewish descent also normally have mildly decreased ANC's¹.

IV) Overview of Other Forms of Leukopenia

a) Eosinopenia⁴ (<0.04 x10⁹/L)
   - Common causes = excess glucocorticoids (stress, Cushing’s, iatrogenic), significant epinephrine release, acute inflammatory state (interleukin-5)

b) Basopenia⁴ (<0.01 x10⁹/L)
   - Common causes= excess glucocorticoids, acute inflammation, hyperthyroidism

c) Monocytopenia⁴ (<0.2 x10⁹/L)
   - Usual cause= prednisone administration, w/i first 12h

V) A Note on Clinical Presentation¹

- Sometimes the only clinical clue that points towards neutropenia is infection that may be severe and/or recurrent. However...
  1) In certain situations/conditions neutropenic pts may not be particularly more prone to infection
  2) Neutropenic pts with infection may not mount the usual immune response and can thus have unique clinical presentations, e.g. absence of typical pneumonia findings on CXR

Neutropenia Etiology and Work-up Algorithm¹,¹²,¹³,¹⁴

- Please refer to the attached flowchart
- Section A) Isolated Neutropenia with Other Cell Lines (Predominantly) unaffected
- Section B) Non-Isolated Neutropenia (or Leukopenia)
- Legend: AbN=abnormal, Cx=culture, Dx=diagnosis, Hx=history, R/o=rule out, Sx=symptom/sign, Tx=treatment

Management*

- Treat/reverse/address underlying cause, when possible (e.g. bacterial infection, drug-induced, nutritional, SLE)
- Primary autoimmune neutropenia:
  - Targetted tx of neutropenic episodes usually not needed. Spontaneous remission common¹
- Oncology pts with (afebrile) neutropenia⁵:
  - Prophylactic Abx (e.g. fluoroquinolone) for pts thought to be at risk of >7d of very severe neutropenia
  - Prophylactic antifungals in certain high risk pts (e.g. posaconazole for Aspergillus)
- Oncology pts with febrile neutropenia⁵:
  - Empiric tx with broad-spectrum beta lactam Abx, PO rather than IV only if low risk
  - Initiate empiric antifungal therapy if fever persists >3-7d
  - Neutrophil transfusions are sometimes carried out for high risk pts
  - Colony-stimulating factors (CSF’s) may be considered for oncology pts who have neutropenia due to chemotherapy
- (Post)infection-related neutropenia¹:
  - Tends to be short-lived except in some cases relating to Hep B, EBV or HIV¹
  - CSF has been used in AIDS pts with neutropenia & severe infections¹⁵,¹⁶,¹⁷
- Pure white cell aplasia, drug-induced agranulocytosis or SIDS:
  - Focus on: prevention & rapid Tx of infections, broad coverage Abx therapy for fever (even without infectious sx's)¹
- Cyclic neutropenia (CN)⁵:
  - Supportive Tx
  - G-CSF for infection prophylaxis and sometimes for sx reduction
- Congenital neutropenia (non-cyclic):
  - Tx with CSF's if severe recurrent infections occur¹
  - Rarely, hematopoietic cell transplantation may be used if G-CSF fails¹⁸

*Specific management of primary bone marrow and hematological disorders & malignancies goes beyond the scope of this one-pager
Neutropenia Etiology and Work-Up Algorithm – Section A

Finding of neutropenia by CBC & Diff
(Confirmation by manual repeat of diff and/or blood film.)

Immediate heme referral if
1) Neutrophils < 0.5 x 10^9/L
OR
2) Neutrophils 0.5 – 1.0 x 10^9/L and patient has Hx repeated infections
OR
3) Patient has lymphadenopathy

If patient febrile (febrile neutropenia)

Consider clinical features/characteristics to aid dx, for example:
1) Infectious Sx's or diagnoses – current, recent, or cyclic
2) Inflammatory Sx's: e.g. lupus, RA (→ rheum referral)
3) Sx's c/w malignancy: e.g. unexplained weight loss, Hx of fevers, hypercalcemia (→ heme referral)
4) Patient Hx/general characteristics: e.g. neonatal/pediatric, vegan, gastrectomy, EtOH consumption, toxin exposure
5) Medications, Tx's: e.g. chemotherapy, hemodialysis

If no clinical features / clues present

Periodic CBC's (q 3-4 weeks) for 2-3 months for monitoring.

><2-3 months of monitoring AND
If neutropenia continues and no new clinical features emerge to suggest etiology

CBC and check ESR/CRP +/- serology +/- tests for autoantibodies to r/o autoimmune cause

If tests negative, neutropenia stable and no new clinical features

Periodic CBC's q 4-6 months for monitoring.

<2-3 months of monitoring

Consider hospital admission.
- Lytes, Cr, LFTs, Blood Cx's x 2 (from different sites including peripheral vein and indwelling IV, as applicable), coags, CRP/ESR +/- - Urine R&M / C&S +/- - CXR +/- - NP Swab +/- - LP +/- - Stool or skin Cx's - Any Cx's should be taken before rapid initiation of empiric Abx Tx - Consider malignancy Dx, specialist referral

Neutropenia Etiology and Work-Up Algorithm – Section B

If Neutropenia (or leukopenia) and any other CBC abnormality (e.g. AbN Plts +/- AbN Hb +/- abN MCV) at any time:
1) R/o nutritional deficiency
2) Blood film and heme referral (to r/o primary hematological or bone marrow pathology)

References can be found online at http://www.dfcm.utoronto.ca/programs/postgraduateprograme/One_Pager_Project_References.htm